Appendix:

The Appendix includes the following items:

- Information Disclosure Statement of December 17, 2004

- verified English translations of priority document Japanese Application No. 2002-176332 and Japanese Application No. 2002-176333

- Solubility Parameters: Theory and Application, John Burke, The Oakland Museum of California, August 1984, Appeared in the AIC Book and Paper Group Annual, Vol. 3, 1984, Craig Jensen, Editor, pp. 13-58, printout from website http://sul-server-2.stanford.edu/byauth/burke/solpar/

- Solubility Parameters: Theory and Application, John Burke, The Oakland Museum of California, August 1984, Part 2 - The Hildebrand Solubility Parameter, printout from website http://sul-server-2.stanford.edu/byauth/burke/solpar/solpar2.html

- Solubility Parameters: Theory and Application, John Burke, The Oakland Museum of California, August 1984, References, printout from website http://sul-server-2.stanford.edu/byauth/burke/solpar/solpar8.html

- A method for estimating both the solubility parameters and molar volumes of liquids. Robert F. Fedors, *Polymer Engineering & Science*, Volume 14, Issue 2, February 1974, pages 147-154.

[Document Name] Specification

[Title of the Invention] BIOCOMPATIBLE POLYMER

[Claims]

[Claim 1]

A biocompatible polymer comprising 8-45 mol% of a unit originating from a polymerizable monomer having a polyalkylene oxide chain, 30-90 mol% of a unit originating from a polymerizable monomer having a hydrophobic group, and 2-50 mol% of a unit originating from a polymerizable monomer having a hydroxyl group.

[Claim 2]

The biocompatible polymer according to claim 1, wherein the content ratio of the unit originating from the polymerizable monomer having a hydroxyl group to the unit originating from the polymerizable monomer having a hydrophobic group is from 0.05 to 1.0.

[Claim 3]

The biocompatible polymer according to claim 1 or 2, wherein the polymerizable monomer having a hydroxyl group is 2-hydroxyisobutyl (meth)acrylate.

[Claim 4]

The biocompatible polymer according to any one of claims 1-3, wherein the polymer is used for a leukocyte removal filter for removing leukocytes from blood.

[Claim 5]

A selective leukocyte removal filter material comprising polymer described in any one of claims 1-3 on at least the surface of a filter supporting material.

[Detailed Description of the Invention]

[0001]

[Technical field where the invention belongs]

The present invention relates to a polymer having excellent biocompatibility and exhibiting low adherence with platelets. More particularly, the present invention relates to a polymer that can be used for a leukocyte removal filter for selectively removing leukocytes from blood. Furthermore, the present invention also relates to a selective leukocyte removal filter having said polymer on the surface thereof.

[0002]

[Background art]

Following the progress of immunology and blood transfusion in recent years, component transfusion in which only blood components required for treating various diseases are transfused has become more popular than conventional whole blood transfusion. Blood component transfusion is an outstanding transfusion treatment exhibiting a high curative effect, while mitigating the load on patients during transfusion. Various blood preparations used for the blood component transfusion, such as concentrated erythrocytes, concentrated platelets, and platelet poor plasma, are prepared by centrifuging whole blood obtained by donation. However, it has become known that side reactions are induced after transfusion due to the leukocytes contained in these blood preparations because the blood preparations obtained by centrifugation contain many leukocytes. The side reactions after transfusion include comparatively slight side reactions, such as headache, nausea, a chill, and a non-hemolytic exothermic reaction, as well as serious side

reactions such as induction of graft versus host (GVH) reaction to a patient with an immune disorder in which the transfused leukocytes has a death-inducing effect on the skin and internal organs of the recipient, infection by viruses present in leukocytes such as cytomegalovirus infection, and alloantigen sensibilization. Removing leukocytes from the blood preparations is effective in preventing such side reactions after transfusion.

[0003]

There has been an increasing demand for the technology of selectively removing leukocytes from patient's peripheral blood for medical treatment of systemic erythematodes, chronic or malignant rheumatoid arthritis, disseminated sclerosis, chronic ulcerative colitis, Crohn's disease, leukemia, and cancer and for the purpose of immune suppression before transplant. Leukocyte removal is practiced also in the field of heart surgery, wherein leukocytes are removed from the blood perfused after coronary-artery bypass surgery to mitigate a hindrance effect by activated leukocytes.

[0004]

Methods for removing leukocytes from blood are broadly classified into a centrifuge separation method, making use of differences in the specific gravity of blood components, and a filter method using a fibrous medium such as non-woven fabric or a porous sponge-like material having three-dimensional continuous pore networks as a filter. The filter method is more popular due to higher leukocyte removal efficiency, simple procedure, and lower cost.

[0005]

Polymer materials constructing these leukocyte-removal filters are generally hydrophobic and has high adherence with other useful blood components such as platelets. It has been difficult to achieve a balance between the leukocyte-removal efficiency and the platelet recovery efficiency. Development of a material that can selectively remove leukocytes, while allowing platelets to pass through, has been strongly desired, particularly for patients with a disease, which is need to be supplied platelets, such as anaplastic anemia, idiopathic thrombocytopenic purpura or leukemia.

[0006]

When an aqueous-type liquid containing platelets such as blood is caused to come in contact with a material, the higher the hydrophilicity of the surface of the material, the more difficult it is for the platelets to become activated and the easier it is for a water layer to be formed on the material surface by the hydrogen bond of water and the material, whereby there are provided advantages that adsorption of platelets and hydrophobic proteins can be inhibited. Therefore, various hydrophilic polymers have been developed to modify the surface of materials and methods for introducing such polymers onto the surface of materials by graft polymerization or coating are known in the art. JP-A 2000-245833 discloses a filter material for selectively removing leukocytes. The material allows erythrocytes and platelets to pass through, but does not allow leukocytes to pass through. In the filter material, the above problems have been overcome by coating a hydrophilic polymer onto the material forming the filter. One possible problem with the coated filter material is elution of the hydrophilic polymer.

Although the possibility of the polymer elution into an aqueous solution is very low, a material with a smaller risk of elution has been desired for use in processing of a large amount of blood, such as that used for extracorporeal circulation, to ensure stability of the filter material when it is kept in contact with an aqueous solution such as blood for a long time.

[0007]

JP-A 05-262656 discloses a leukocyte removal filter which has polymer containing alkoxy(meth)acrylate as a main component on the surface of the filter. The filter aim to prevent the adhere with platelets and to selectively remove leukocytes by using alkoxy(meth)acrylate. However, it takes the time for priming due to the low hydrophilicity, and a possibility of clogging may be high. Further, no example using fresh whole blood is described in this JP-A 05-262656. The present inventors have confirmed that not only the flowability of the blood is poor, but also the platelet recovery rate becomes low and the objective products cannot be obtained when treating the whole blood by using the polymer in substance.

[0008]

There has been no high performance polymers used for filters for selective removal of leukocytes exhibiting both high safety and high blood filtration performance.

[0009]

[Problems to be solved by the invention]

An object of the present invention is to provide a novel polymer having an extremely low elution property and excellent biocompatibility, useful for a leukocyte removal filter which aims to selectively remove leukocytes from various bloods,

particularly from whole blood, while preventing adsorption of platelets as much as possible. Specifically, the object of the present invention is to provide a novel polymer that can be effectively used for platelet transfusion or extracorporeal circulation for leukocyte removal, excelling in biocompatibility, exhibiting only a low adsorption to platelets, and having a low elution property. Other object of the present invention is also to provide a selective leukocyte removal filter which has excellent biocompatibility and low adsorption to platelets.

[0010]

[Means for solving the problems]

As a result of extensive studies to resolve the above problems, the present inventors have found that a polymer comprising a unit originating from a polymerizable monomer having a polyalkylene oxide chain, a unit originating from a polymerizable monomer having a hydrophobic group, and a unit originating from a polymerizable monomer having a hydroxyl group at a specific ratio of the three units originating from the above polymerizable monomers surprisingly exhibits remarkably low elution property, excellent biocompatibility, particularly low adsorption to platelets, and excellent selective leukocyte removal capability. This finding has led to the completion of the present invention.

[0011]

Specifically, the present invention provides a biocompatible polymer comprising a unit originating from a polymerizable monomer having a polyalkylene oxide chain, a unit originating from a polymerizable monomer having a hydrophobic

group, and a unit originating from a polymerizable monomer having a hydroxyl group, concretely 8-45 mol% of a unit originating from a polymerizable monomer having a polyalkylene oxide chain, 30-90 mol% of a unit originating from a polymerizable monomer having a hydrophobic group, and 2-50 mol% of a unit originating from a polymerizable monomer having a hydroxyl group, wherein the total of the three types of monomer units is 100 mol%.

[0012]

The polyalkylene oxide chain used in the present invention refers to a repeating structure in which an alkyl group having 2 to 4 carbon atoms and an oxygen atom bond alternately. The polyalkylene oxide chain includes, for example, a polyethylene oxide chain, polypropylene oxide chain, polybutylene oxide chain, or the like. The polyalkylene oxide chain in the polymer exhibits a high platelet adsorption preventing effect due to the excellent compatibility with blood possessed by the polyalkylene oxide chain. The repeating number of the alkylene oxide chain used in the present invention is preferably in range from 2 to 10. If the number of repeating units is less than 2, it is difficult to obtain a sufficient platelet adsorption preventing effect. If the number of is repeating units more than 10, the polymer becomes less adhesive to the law material of the filter, thereby increasing a tendency of the polymer eluting more easily. The number of repeating units is preferably 2 to 6, and more preferably 2 to 4.

[0013]

Examples of the polymerizable monomer having the polyalkylene oxide chain include, but are not limited to, methoxydiethylene glycol (meth)acrylate, ethoxydiethylene

glycol (meth)acrylate, methoxydipropylene glycol (meth)acrylate, ethoxydipropylene glycol (meth)acrylate, methoxytriethylene glycol (meth)acrylate, methoxytripropylene glycol (meth)acrylate, ethoxytriethylene glycol (meth)acrylate, ethoxytripropylene glycol (meth)acrylate, methoxytetraethylene glycol (meth)acrylate, methoxytetrapropylene glycol (meth)acrylate, ethoxytetraethylene glycol (meth)acrylate, ethoxytetrapropylene glycol (meth)acrylate, methoxydiethylene glycol vinyl ether, ethoxydiethylene glycol vinyl ether, methoxytriethylene glycol vinyl ether, and ethoxytriethylene glycol vinyl ether. Of these, (meth)acrylate having a polyethylene glycol chain such as methoxydiethylene glycol (meth)acrylate, ethoxydiethylene glycol (meth)acrylate, methoxytriethylene glycol (meth)acrylate, ethoxytriethylene glycol (meth)acrylate, methoxytetraethylene glycol (meth)acrylate, and ethoxytetraethylene glycol (meth)acrylate are preferably used due to the high platelet adsorption preventing effect. Methoxydiethylene glycol (meth)acrylate is most preferable from the viewpoint of easy availability, easy handling, easy polymerization, and the like. The (meth)acrylate in the present invention refers to acrylate and/or methacrylate.

[0014]

It is necessary for the polymer of the present invention to contain the unit originating from the polymerizable monomer having a polyalkylene oxide chain in an amount from 8 mol% to 45 mol%. If less than 8 mol%, the platelet adsorption preventing effect of the polyalkylene oxide chain is insufficient,

resulting in reduced platelet recovery performance. If more than 45 mol%, the hydrophobicity of the polymer decreases, giving rise to easy elution of the polymer when coming into contact with an aqueous solution such as blood. The amount of the unit is preferably from 20 mol% to 40 mol%, and more preferably from 25 mol% to 35 mol%.

[0015]

The term "unit" in the present invention refers to a minimum recurring unit in a polymer molecule originating from respective polymerizable monomers. For example, in the case of the addition polymerization of a polymerizable monomer of a vinyl compound with the formula CH_2=CXY (wherein X is H or a substituent other than H and Y is a substituent other than X) by simply opening the double bond, the minimum recurring unit is -(CH_2-CXY)-. In the case where the polymer is synthesized by polycondensation from a polymer precursor of the formula A-(R)-B, wherein R indicates a part not released in the polymerization and A and B are releasable parts during the polymerization reaction, -(R)- is the minimum recurring unit.

[0016]

The term "polymerizable monomer having a hydrophobic group" in the present invention refers to a polymerizable monomer having solubility in water at 20°C of 0 wt% or more and less than 50 wt%, and not containing a polyalkylene oxide chain and a hydroxyl group in the molecule. The unit originating from a polymerizable monomer having a hydrophobic group has effects of decreasing the solubility of the polymer in an aqueous solution, preventing elution of the polymer, and increasing leukocyte removal performance.

[0017]

The solubility can be determined by a known method such as a dew point method, thermal analysis, electric method comprising measurement of the electromotive force or electric conductivity of the solution, gas chromatography analysis, and tracer method in the case where the monomer is a solid. When the monomer is a liquid, the solubility can be determined by, in addition to the methods applied to a solid monomer, a capacitance method, light scattering method, vapor pressure method, or the like, all of which are known in the art. As a simpler method, when the monomer has a boiling point sufficiently higher than the boiling point of water, a method of vaporizing water from a saturated solution of the monomer and measuring the weight of the residue can be used.

[0018]

As examples of the above-mentioned strong hydrophobic polymerizable monomer, styrene, methylstyrene, butyl (meth)acrylate, isobutyl (meth)acrylate, propyl (meth)acrylate, isopropyl (meth)acrylate, ethyl (meth)acrylate, methyl (meth)acrylate, phenyl (meth)acrylate, ethylhexyl (meth)acrylate, and vinyl acetate can be given. Of these, alkyl (meth)acrylates such as butyl (meth)acrylate, isobutyl (meth)acrylate, propyl (meth)acrylate, isopropyl (meth)acrylate, ethyl (meth)acrylate, and methyl (meth)acrylate are preferably used due to their adequately hydrophobic and easily polymerizable properties. Methyl (meth)acrylate is most preferable from the viewpoint of high biological safety.

[0019]

It is necessary for the polymer of the present invention to contain the unit originating from the polymerizable monomer having a hydrophobic group in an amount from 30 mol% to 90 mol%. If less than 30 mol%, the hydrophobicity of the polymer decreases, giving rise to easy elution of the polymer when coming into contact with an aqueous solution such as blood. If more than 90 mol%, the hydrophobicity of the polymer increases, giving rise to increased adsorption of platelets to the surface of the filter material. The amount of the unit is preferably from 35 mol% to 80 mol%, and more preferably from 40 mol% to 70 mol%.

[0020]

The term "polymerizable monomer containing a hydroxyl group" as used in the present invention refers to a polymerizable monomer having a hydroxyl group, but not containing a polyalkylene oxide chain in the molecule. The polymerizable monomer having a hydroxyalkyl group, such as a hydroxymethyl group, hydroxyethyl group, hydroxypropyl group, hydroxybutyl group, or the like, can be suitably used, as the monomer exhibits appropriate spacer effect and hydrophilicity of the main chain of the polymer. As the polymerizable monomers containing a hydroxyl group,

2-hydroxyethyl (meth)acrylate, 2-hydroxypropyl (meth)acrylate, 3-hydroxypropyl (meth)acrylate, 2-hydroxyisobutyl (meth)acrylate, 3-hydroxyisobutyl (meth)acrylate, 2-hydroxybutyl (meth)acrylate, 3-hydroxybutyl (meth)acrylate, and 4-hydroxybutyl (meth)acrylate can be given. Among them, 2-hydroxyethyl (meth)acrylate, 2-hydroxypropyl (meth)acrylate, 2-hydroxyisobutyl (meth)acrylate, are preferable, due to the appropriate spacer effect of the main

chain of the polymer. Furthermore, 2-hydroxyisobutyl (meth)acrylate is most preferable in the view of exhibiting appropriate hydrophilicity due to having tertiary hydroxyl group.

[0021]

It is necessary for the polymer of the present invention to contain the unit originating from the polymerizable monomer having a hydroxyl group in an amount from 2 mol% to 50 mol%. If less than 2 mol%, the hydrophilicity of the polymer decreases, giving rise to increased adsorption of platelets to the surface of the filter material. If more than 50 mol%, the hydrophobicity of the polymer decreases, giving rise to easy elution of the polymer when coming into contact with an aqueous solution such as blood. The amount of the unit is preferably from 5 mol% to 40 mol%, and more preferably from 10 mol% to 30 mol%.

[0022]

The content ratio of the unit originating from the polymerizable monomer having a hydroxyl group to the unit originating from the hydrophobic polymerizable monomer in the polymer of the present invention is preferably from 0.05 to 1. If the content ratio is less than 0.05, the hydrophilicity provided by hydroxyl groups is canceled by hydrophobic groups and the hydrophilicity of the polymer decreases, giving rise to increased adsorption of platelets to the surface of the filter material. If more than 1, the elution preventive effect of the hydrophobic groups is canceled by hydroxyl groups and hydrophobicity of the polymer decreases, giving rise to easy elution of the polymer when coming into contact with an aqueous solution such as blood. The content ratio is preferably from

0.1 to 0.9, and more preferably from 0.15 to 0.8.

[0023]

The chemical composition of a polymer can be determined by extracting the polymer using an appropriate solvent which does not dissolve the base material of the filter and analyzing the extract by a known method such as NMR spectrum, IR spectrum, and elemental analysis. When the polymer is not dissolved, in addition to the above-mentioned methods, known surface analytical methods such as X-ray photoelectron spectroscopy (ESCA) and a method of using an electron probe X-ray microanalyser (EPMA) can be used.

[0024]

The polymer of the present invention preferably has a weight average molecular weight (Mw) in the range of 50,000 to 3,000,000. If the Mw is less than 50,000, the molecular weight of the polymer decreases when the polymer is sterilized, particularly by radiation, giving rise to an increase in the eluted amount. If the weight average molecular weight (Mw) is more than 3,000,000, solubility of the polymer in the solvent used for coating decreases. In addition, there may be the case where the polymer cannot be produced in a stable manner. The Mw is more preferably from 100,000 to 2,000,000, and most preferably from 200,000 to 1,500,000. Although the Mw can be determined by various known methods, a value determined by gel permeation chromatography (hereinafter abbreviated to GPC) using polymethyl methacrylate as a standard was used in the present invention.

[0025]

The polymer may be either a random copolymer or a block

copolymer. The random copolymer is, however, more preferable since the block copolymer may have a tendency of decreasing the solubility in a solvent when used for coating and may have a tendency of impairing coating uniformity due to micelle formation in the solution. . As the form of the polymer molecule chain, a linear polymer is more preferable since a branched polymer may have a tendency of decreasing the solubility in a solvent when used for coating and may have a tendency of impairing coating uniformity due to micelle formation in the solution. .

[0026]

A common polymerization method can be employed for synthesizing the polymer of the present invention. Addition polymerization (vinyl polymerization) and the like involving chain reactions; isomerization polymerization; and dissociation reaction, polyaddition, polycondensation, addition polycondensation, and the like involving consecutive reactions may be employed. Radicals, ions, and the like can be used as chain carriers in producing the polymer.

[0027]

As the type of polymerization, solution polymerization, mass polymerization, deposition polymerization, emulsion polymerization, and the like can be given. Of these, solution polymerization is preferable. An example of the polymerization method is given below. A special grade ethanol solution in which each monomer or a diazo initiator is dissolved is added dropwise to ethanol used as a polymerization solvent while stirring at a constant temperature below the boiling point of ethanol in a nitrogen atmosphere. A stabilizer and the like may be added

as appropriate. The reaction yield is measured and confirmed by using a known method such as gas chromatography.

[0028]

The reaction product may be purified by a common chemical purification method to remove impurities such as low molecular weight components and unreacted materials which are contained in the polymer or the reaction solution containing the polymer. As the purification method, a method comprising dissolving the reaction mixture in a solvent that dissolves the impurities, but does not dissolve the polymer, to cause the polymer to precipitate, and separating the precipitate (polymer) by filtration, decantation, or the like can be given. As required, the precipitate is washed with a solvent with solubility slightly higher than that of the precipitation solvent (a mixture of the precipitation solvent and a solvent, for example) and the precipitate is dried under reduced pressure until the weight of the precipitate becomes constant, thereby obtaining a solid polymer.

[0029]

The polymer of the present invention can be suitably used, in the view of increasing the biocompatibility of a medical material when coated on the surface. For example, the polymer can be used for artificial organs such as an artificial blood vessel, artificial kidney, and artificial liver, blood cell separation filters such as a leukocyte removal filter, dialysis membrane, anti-thrombus material, and the like. In particular, since the polymer can selectively remove leukocytes from blood, that is, a concentrated erythrocyte preparation, concentrated platelet preparation, platelet poor plasma preparation,

peripheral blood, cell floating solutions containing leukocytes and platelets such as lymph and marrow fluid, the polymer can be suitably used for a selective leukocyte removal filter of blood preparations and a selective leukocyte removing device for extracorporeal circulation. In addition, since the polymer is eluted only with difficulty and is stable even if caused to be in contact with an aqueous solution for a long period of time, the polymer can be most suitably used for selective leukocyte removal apparatus for extracorporeal circulation designed to process a large amount of blood.

[0030]

The filter material which can be suitably used for the selective leukocyte removal filter and the selective leukocyte removing device for extracorporeal circulation may be obtained by having the polymer of the present invention present at least on the surface of the supporting material constituting the filter. The term "having the polymer present at least on the surface of the supporting material" indicates the polymer is present on the surface of the supporting material substantially covering the surface. As the method for having the polymer present on the surface of filter, known methods such as a method of coating or depositing and insolubilizing the polymer on the supporting material, a method of phase-separating the polymer from the supporting material during fabrication, and the like can be used. Of these, the method of coating is most preferable due to the easy industrial applicability and excellent performance stability.

[0031]

The polymer of the present invention can be coated to

polymeric material, such as polyester, polyolefin, polyacrylonitrile, polyamide, polystyrene, polyalkyl (meth)acrylate, polyvinyl chloride, polychloroprene, polyurethane, polyvinyl alcohol, polyvinyl acetate, polysulfone, polyether sulfone, polybutadiene, butadiene-acrylonitrile copolymer, styrene-butadiene copolymer, ethylene-vinyl alcohol copolymer, cellulose diacetate, and ethyl cellulose. Of these, polyester and polyolefin are preferable, with a particularly preferable organic filter material being polyester, but are not limited to the above exemplification, if the polymeric material is used for the object of the present invention.

[0032]

In the present invention various methods can be used for coating the polymer onto the material without any specific limitations inasmuch as the surface properties of the medical material is not largely affected and the surface of the material can be coated with a certain degree of uniformity. Examples of the method for coating the polymer of the present invention onto the filter material include, but are not limited to, a method of impregnating the filter material with a polymer solution, a method of spraying the polymer solution to the filter material, and a method of applying or transcribing the polymer solution to the filter material using a rotogravure roll or the like. Of these methods, the method of impregnating the filter material with a polymer solution and the method of applying or transcribing the polymer solution to the filter material using a rotogravure roll are preferable due to the excellent continuous productivity and low cost.

[0033]

In the case of proceeding the coating onto medical material for the purpose described above various solvents that do not dissolve the law medical material to a noticeable degree can be used as the solvent to dissolve the polymer without any specific limitations. Examples of such a solvent which can dissolve the polymer of the invention include, but are not limited to, water and aqueous solutions containing an inorganic salt, alcohols such as methanol, ethanol, propanol, and butanol, ketones such as acetone and methyl ethyl ketone, esters such as methyl acetate and ethyl acetate, hydrocarbons such as benzene and cyclohexane, halogenated hydrocarbons such as chloroform and dichloromethane, sulfur-containing solvents such as dimethyl sulfoxide, amides such as dimethylformamide and dimethylacetamide, and mixtures of two or more of the above solvents to the extent possible.

[0034]

The concentration of the polymer solution used for coating is preferably 0.001 wt% or more, but less than 10 wt%. If the concentration is less than 0.001 wt%, the amount of the polymer on the surface of the material is too small for the filter material to exhibit sufficient biocompatibility such as properties of preventing platelet adsorption. If the concentration is 10 wt% or more, on the other hand, not only does the solution have too great a viscosity to be handled with ease, but also the surface properties of the medical material may be significantly affected. In addition, such a high concentration is too expensive to be efficiently used. For these reasons, the polymer concentration is more preferably

0.005 wt% or more, but less than 7 wt%, and most preferably 0.01 wt% or more, but less than 5 wt%. The coated amount onto the material is preferably 0.001 wt% or more, but less than 10 wt% in weight variation. A more preferable amount is 0.005 wt% or more, but less than 7 wt%, with the amount of 0.01 wt% or more, but less than 5 wt% being most preferable.

[0035]

To dry the polymer solution after coating, a method comprising removing excess solvent by mechanical compression, by gravity, or by injecting gas such as air or nitrogen, and treating the coated material in dry air or under reduced pressure at atmospheric temperature or with heating can be employed.

[0036]

The present invention is described below by examples, which should not be construed as limiting the present invention.

[Example 1]

(Synthesis of polymer)

One example of the method of synthesizing the polymer used for preparing a selective leukocyte removal filter by coating will be shown. A reaction vessel equipped with a reflux condenser was charged with ethanol (277 ml). After bubbling nitrogen into ethanol and stirring the mixture at 73°C for one hour, monomers were added dropwise over 120 minutes while maintaining a nitrogen atmosphere. An initiator solution was added dropwise at the same time over 300 minutes. After completion of the addition of the initiator solution, the monomers were polymerized for further two hours. The polymerizable monomer mixture was a liquid containing 4.8 g (30.0 mmol) of methoxydiethylene glycol methacrylate (MDG), which is

a polymerizable monomer having an alkylene oxide chain, 4.3 g (50.0 mmol) of methylmethacrylate (MMA), which is a polymerizable monomer having a hydrophobic group, and 2.7 g (20.0 mmol) of 2-hydroxyisobutyl methacrylate (HBMA), which is a polymerizable monomer having a hydroxyl group. The molar ratio of charging the monomers was 30 mol% of MDG, 50 mol% of MMA, and 20 mol% of HBMA. An ethanol solution containing 0.034 g of azobisdimethylvaleronitrile (V-65) was used as the initiator solution. The reaction mixture was added dropwise to purified water to cause the polymer to precipitate. The recovered polymer precipitate was cut into pieces and once again put into purified water, followed by stirring for one hour to wash the polymer. Next, the washed polymer was dried under vacuum at 60°C to obtain the target polymer. The composition of the resulting polymer was analyzed from the integral value of NMR measurement, confirming that the composition was almost in agreement with the charged monomer composition. The weight average molecular weight of the polymer measured by GPC was 6.8×10^5.

[0037]

(Preparation of filter material)

A method of preparing the filter material for selectively removing leukocytes will be described below. 1 g of the polymer obtained was dissolved in 100 ml of a mixed solvent of ethanol and purified water (ethanol:water=70:30). A nonwoven fabric made from polyethylene terephthalate was immersed in the solvent. After removing excessive liquid, the nonwoven fabric was dried at room temperature for 16 hours to obtain the target filter. The average fiber diameter of the filter material was 2.7 μm, the weight per square meter was 90 g/m^2, and the thickness was

0.42 mm.

[0038]

(Elution test)

The method of the elution test is described as follows. A 200 ml container was packed with 15 g of the filter material as above prepared, a physiological saline solution was filled into the container, and γ-ray sterilization (irradiation dose: 25 kGy) was conducted. To confirm elution in the temperature range possibly occurring during actual preservation of medical devices, the container was allowed to stand at 25°C for 24 hours, then at 4°C for 24 hours. The appearance of the filled solution after preservation was observed to confirm that the solution was transparent and colorless, with no change as compared with the state before sterilization.

[0039]

(Evaluation of blood properties (blood performance test))

Next, a test method for evaluating the leukocyte removal rate and platelet recovery rate will be described. The filter material prepared in the above was cut into disks, each with a diameter of 6.8 mm. Seven sheets of the disks were laminated in a 1 ml column having an inlet port and an outlet port. The column was filled with a physiological saline solution and sterilized with γ-ray (irradiation dose: 25 kGy) to prepare the column for performance evaluation. 3 ml of fresh human blood (number of leukocytes: 4,500-8,400/l, number of platelets: 150,000-440,000/μl) to which ACD-A was added as an anti-coagulator (blood:ACD-A=8:1) was fed into the column from the inlet port using a syringe pump at a constant flow rate of 0.5 ml/min. The processed blood was recovered. The leukocyte

concentration and platelet concentration in the blood before and after passing through the column were measured using an automatic blood cell counter (Sysmex SF-3000, manufactured by Toa Medical Electronics Co., Ltd.), and the leukocyte removal rate and the platelet recovery rate were calculated by the following equations.

Leukocyte removal rate (%)
= (1-Leukocyte concentration in the outlet port side blood/Leukocyte concentration in the inlet port side blood) x 100

Platelet recovery rate (%)
= (Platelet concentration in the outlet port side blood /Platelet concentration in the inlet port side blood) x 100

As a result, the leukocyte removal rate was 97.5% and the platelet recovery rate was 85.0%, confirming selective leukocyte removal capability.

[0040]

[Example 2]

A polymer was synthesized in the same manner as in Example 1, except for using 40.0 mol% of MDG, 50.0 mol% of MMA, and 10 mol% of HBMA as the charged monomer composition. The composition of the resulting polymer was analyzed from the integral value of NMR measurement, confirming that the composition was almost in agreement with the charged monomer composition. The weight average molecular weight of the polymer measured by GPC was 8.7×10^5.

A filter material was prepared from the polymer in the same manner as in Example 1. The average fiber diameter of the filter material was 2.7 μm, the weight per square meter was 90 g/m^2, and the thickness was 0.42 mm.

Using the obtained filter material, the elution test and the blood performance test were carried out in the same manner as in Example 1. The appearance of the filled solution after sterilization and preservation confirmed that the solution was transparent and colorless, with no change as compared with the state before sterilization. The leukocyte removal rate was 97.0% and the platelet recovery rate was 85.0%, confirming selective leukocyte removal capability.

[0041]

[Example 3]

A polymer was synthesized in the same manner as in Example 1, except for using 20 mol% of MDG, and 20 mol% of HBMA as the charged monomer composition. The composition of the resulting polymer was analyzed from the integral value of NMR measurement, confirming that the composition was almost in agreement with the charged monomer composition. The weight average molecular weight of the polymer measured by GPC was 9.2 x 10^5. A filter material was prepared from the obtained polymer in the same manner as in Example 1. The average fiber diameter of the filter material was 2.7 μm, the weight per square meter was 90 g/m^2, and the thickness was 0.42 mm.

Using the obtained filter material, the elution test and the blood performance test were carried out in the same manner as in Example 1. The appearance of the filled solution after

sterilization and preservation confirmed that the solution was transparent and colorless, with no change as compared with the state before sterilization. The leukocyte removal rate was 91.7% and the platelet recovery rate 69.0%, confirming selective leukocyte removal capability.

[0042]

[Example 4]

A polymer was synthesized in the same manner as in Example 1, except for using n-butyl methacrylate (BMA) as a polymerizable monomer having a hydrophobic group and 2-hydroxyisopropyl methacrylate (HPMA) as a polymerizable monomer having a hydroxyl group, and charging 20 mol% of MDG, 50 mol% of BMA, and 30 mol% of HPMA as the monomer composition. The composition of the resulting polymer was analyzed from the integral value of NMR measurement, confirming that the composition was almost in agreement with the charged monomer composition. The weight average molecular weight of the polymer measured by GPC was 1.1×10^5.

A filter material was prepared from the polymer in the same manner as in Example 1. The average fiber diameter of the filter material was 2.7 μm, the weight per square meter was 90 g/m^2, and the thickness was 0.42 mm.

Using the obtained filter material, the elution test and the blood performance test were carried out in the same manner as in Example 1. The appearance of the filled solution after sterilization and preservation confirmed that the solution was transparent and colorless, with no change as compared with the state before sterilization. The leukocyte removal rate was 93.8% and the platelet recovery rate was 83.7%, confirming

selective leukocyte removal capability.

[0043]

[Comparative Example 1]

A polymer was synthesized in the same manner as in Example 1, except for using 90.0 mol% of MDG, and 10.0 mol% of MMA as the charged monomer composition. The composition of the resulting polymer was analyzed from the integral value of NMR measurement, confirming that the composition was almost in agreement with the charged monomer composition. The weight average molecular weight of the polymer measured by GPC was 3.5×10^5. A filter material was prepared from the polymer in the same manner as in Example 1. The average fiber diameter of the filter material was 2.7 μm, the weight per square meter was 90 g/m^2, and the thickness was 0.42 mm.

Using the obtained filter material, the elution test and the blood performance test were carried out in the same manner as in Example 1. The filled solution after sterilization and preservation was turbid, confirming that the polymer eluted during sterilization and preservation. In the evaluation of blood properties, the leukocyte removal rate was 97.0% and the platelet recovery rate 78.0%, confirming selective leukocyte removal capability.

[0044]

[Comparative Example 2]

A polymer was synthesized in the same manner as in Example 1, except for using 5.0 mol% of MMA and 95.0 mol% of HBMA as the charged monomer composition. The composition of the resulting polymer was analyzed from the integral value of NMR measurement, confirming that the composition was almost in

agreement with the charged monomer composition. The weight average molecular weight of the polymer measured by GPC was 1.5 x 10^5.

A filter material was prepared from the polymer in the same manner as in Example 1. The average fiber diameter of the filter material was 2.7 μm, the weight per square meter was 90 g/m^2, and the thickness was 0.42 mm.

Using the obtained filter material, the elution test and the blood performance test were carried out in the same manner as in Example 1. The filled solution after sterilization and preservation was turbid, confirming that the polymer eluted during sterilization and preservation. In the blood performance, the leukocyte removal rate was 88.3% and the platelet recovery rate was 51.9%, confirming a slightly low platelet recovery rate.

[0045]

[Comparative Example 3]

A polymer was synthesized in the same manner as in Example 1, except for using 40.0 mol% of MDG, 25.0 mol% of MMA, and 35.0 mol% of HBMA as the charged monomer composition. The composition of the resulting polymer was analyzed from the integral value of NMR measurement, confirming that the composition was almost in agreement with the charged monomer composition. The weight average molecular weight of the polymer measured by GPC was 4.2 x 10^5.

A filter material was prepared from the polymer in the same manner as in Example 1. The average fiber diameter of the filter material was 2.7 μm, the weight per square meter was 90 g/m^2, and the thickness was 0.42 mm.

Using the obtained filter material, the elution test and the blood performance test were carried out in the same manner as in Example 1. The filled solution after sterilization and preservation was turbid, confirming that the polymer eluted during sterilization and preservation. In the evaluation of blood properties, the leukocyte removal rate was 85.8% and the platelet recovery rate was 72.7%.

[0046]

[Comparative Example 4]

A polymer was synthesized in the same manner as in Example 1, except for using 100.0 mol% of methoxyethylene glycol methacrylate (MEGM) as unit originating from a polymerizable monomer having a polyalkylene oxide chain. The weight average molecular weight of the polymer measured by GPC was 9.1×10^4.

A filter material was prepared from the polymer in the same manner as in Example 1. The average fiber diameter of the filter material was 2.7 μm, the weight per square meter was 90 g/m^2, and the thickness was 0.42 mm.

Using the prepared filter material, the elution test and the blood performance test were carried out in the same manner as in Example 1. The filled solution after sterilization and preservation was turbid, confirming that the polymer eluted during sterilization and preservation. In the blood performance, the leukocyte removal rate was 98.3% and the platelet recovery rate was 19.1%, confirming a low platelet recovery rate.

[0047]

[Comparative Example 5]

A polymer was synthesized in the same manner as in Example

1, except for using methoxynonaethylene glycol methacrylate (MNG) as a polymerizable monomer having a polyalkylene oxide chain and charging 65.0 mol% of MNG and 35.0 mol% of MMA as the charged monomer composition. The composition of the resulting polymer was analyzed from the integral value of NMR measurement, confirming that the composition was almost in agreement with the charged monomer composition. The weight average molecular weight of the polymer measured by GPC was 2.2×10^5.

A filter material was prepared from the polymer in the same manner as in Example 1. The average fiber diameter of the filter material was 2.7 μm, the weight per square meter was 90 g/m^2, and the thickness was 0.42 mm.

Using the obtained filter material, the elution test and the blood performance test were carried out in the same manner as in Example 1. The filled solution after sterilization and preservation was turbid, confirming that the polymer eluted during sterilization and preservation. The leukocyte removal rate was 99.5% and the platelet recovery rate was 52.0%, confirming a low platelet recovery rate.

[0048]

These above results are summarized in Table 1.

[Table 1]

	Example				Comparative Example				
	1	2	3	4	1	2	3	4	5
Polymerizable monomer having polyalkylene oxide chain (mol %)	30	40	20	20	90	0	40	100	65
Polymerizable monomer having a hydrophobic group (mol %) A	50	50	60	50	10	5	25	0	35
Polymerizable monomer having hydroxyl group (mol %) B	20	10	20	30	0	95	35	0	0
B/A	0.40	0.20	0.33	0.6	0	19.0	1.4	-	0
Elution test: Filling solution appearance	Tp*	Tp	Tp	Tp	Cl*	Cl	Cl	Cl	Cl
Blood performance test:									
Leukocyte removal rate (%)	97.5	97.0	98.5	93.8	97.0	88.3	85.8	97.0	99.5
Platelet recovery rate (%)	85.0	85.0	89.4	83.7	78.0	51.9	72.7	78.0	52.0

* Tp: Transparent and colorless, Cl: Cloudy

[0049]

As can be seen from Table 1, the filter materials using a polymer comprising a unit originating from a polymerizable monomer having a polyalkylene oxide chain, a unit originating from a polymerizable monomer having a hydrophobic group, and a unit originating from a polymerizable monomer having a hydroxyl group at a specific ratio of these units originating from the three polymerizable monomers were confirmed to elute only a minimal amount of polymer components and to exhibit selective leukocyte removal capability. On the other hand, the filter materials using a polymer not meeting these conditions did not satisfy either the elution test or the blood performance test, or both.

[0050]

[Effects of the invention]

The biocompatible polymer of the present invention has a low elution property and suppresses the adhesion of platelet as much as possible and is thus useful for the selective leukocyte removal filter which can selectively remove leukocytes. When the biocompatible polymer of the present invention is used for the selective leukocyte removal filter for preparing a blood product or the selective leukocyte removing device for extracorporeal circulation, remarkable effects exhibiting a low elution but high platelet recovery rate and high leukocyte removal rate can be given.

[Document Name] Abstract

[Abstract]

[Problems] The present invention is to provide a noble polymer having a very low elution property and exhibiting an excellent biocompatible property, particularly to provide a polymer useful for selective leukocyte removal filter suppressing the adhesion of platelet in various blood products as much as possible, and selectively removing leukocytes. Furthermore, the present invention is to provide a selective leukocyte removal filter having an excellent biocompatible property and low platelet-adhering property using said polymer.

[Means for solving] A polymer having an low elution property, and excelling in biocompatibility can be obtained by comprising 8-45 mol% of a unit originating from a polymerizable monomer having a polyalkylene oxide chain, 30-90 mol% of a unit originating from a polymerizable monomer having a hydrophobic group, and 2-50 mol% of a unit originating from a polymerizable monomer having a hydroxyl group.

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[Name of Submission]	Specification	1
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[Document Name] Specification

[Title of the Invention] SELECTIVE LEUKOCYTE REMOVAL FILTER MATERIAL

[Claims]

[Claim 1]

A selective leukocyte removal filter material for selectively removing leukocytes, which has a polymer present at least on the surface of the supporting body, wherein the polymer is a nonionic polymer which comprises a unit originating from a polymerizable monomer having a polyalkylene oxide chain and a unit originating from a hydrophobic polymerizable monomer comprising a strong hydrophobic polymerizable monomer and a weak hydrophobic polymerizable monomer, and the polymer has 10.0 - 11.5 of solubility factor (σ value) and the supporting body having the above polymer has 7.0 - 15.0 of σ value.

[Claim 2]

The selective leukocyte removal filter material according to claim 1, wherein the unit originating from the hydrophobic polymerizable monomer comprises 5-50 mol% of the unit originating from the weak hydrophobic polymerizable monomer.

[Claim 3]

The selective leukocyte removal filter material according to claim 1 or 2, wherein the weak hydrophobic polymerizable monomer is 2-hydroxyisobutyl (meth)acrylate.

[Claim 4]

The selective leukocyte removal filter material according to any one of claims 1-3, wherein the filter material is a woven fabric or nonwoven fabric.

[Claim 5]

A selective leukocyte removal filter comprising the filter material according to any one of claims 1 to 4 packed in a container having at least a blood inlet port and a blood outlet port.

[Detailed Description of the Invention]

[0001]

[Technical field where the invention belongs]

The present invention relates to a selective leukocyte removal filter material for selectively removing leukocytes while allowing erythrocytes and platelets to pass through. In more detail, the present invention relates to a selective leukocyte removal filter material used for the purpose of selectively removing leukocytes in blood during transfusion or extracorporeal circulation.

[0002]

[Background art]

Following the progress of immunology and blood transfusion in recent years, component transfusion in which only blood components required for treating various diseases are transfused has become more popular than conventional whole blood transfusion. Blood component transfusion is an outstanding transfusion treatment exhibiting a high curative effect, while mitigating the load on patients during transfusion. Various blood preparations used for the blood component transfusion are prepared by centrifuging whole blood obtained by donation. However, it has become known that side reactions are induced after transfusion due to the leukocytes contained in these blood preparations because the blood preparations obtained by centrifugation contain many leukocytes. The side reactions after transfusion include comparatively slight side reactions, such as headache, nausea, a chill, and a non-hemolytic exothermic reaction, as well as serious side reactions such as induction of graft versus host (GVH) reaction to a patient with an immune

disorder in which the transfused leukocytes has a death-inducing effect on the skin and internal organs of the recipient, infection by viruses present in leukocytes such as cytomegalovirus infection, and alloantigen sensibilization. Removing leukocytes from the blood preparations is effective in preventing such side reactions after transfusion.

[0003]

There has been an increasing demand for the technology of removing leukocytes from patient's peripheral blood for medical treatment of systemic erythematodes, chronic or malignant rheumatoid arthritis, disseminated sclerosis, chronic ulcerative colitis, Crohn's disease, leukemia, and cancer and for the purpose of immune suppression before transplant. Leukocyte removal is practiced also in the field of heart surgery, wherein leukocytes are removed from the blood perfused after coronary-artery bypass surgery to mitigate a hindrance effect by activated leukocytes.

[0004]

Methods for removing leukocytes from blood are broadly classified into a centrifuge separation method, making use of differences in the specific gravity of blood components, and a filter method using a fibrous medium such as non-woven fabric or a porous sponge-like material having three-dimensional continuous pore networks as a filter. The filter method is more popular due to higher leukocyte removal efficiency, simple procedure, and lower cost.

[0005]

The many of the above filter materials comprises hydrophobic polymer materials, and same time cause other blood

component, particularly useful platelet to rise adhesion thereof. Therefore, it has been difficult to achieve a balance between the leukocyte-removal efficiency and the platelet recovery efficiency of the filter material. Development of a filter material that can selectively remove leukocytes, while allowing platelets to pass through, has been strongly desired for patients with a disease, who desire to be supplied platelets, such as anaplastic anemia, leukemia, or the like.

[0006]

When an aqueous-type liquid containing platelets such as blood is caused to come in contact with a material, the higher the hydrophilicity of the surface of the material, the more difficult it is for the platelets to become activated and the easier it is for a water layer to be formed on the material surface by the hydrogen bond of water and the material, whereby there are provided advantages that adsorption of platelets and hydrophobic proteins can be inhibited. Therefore, various hydrophilic polymers have been developed to modify the surface of materials and methods for introducing such polymers onto the surface of materials by graft polymerization or coating are known in the art. JP-A 2000-245833 discloses a leukocyte removal filter material comprising fiber having nonionic hydrophilic group. In the filter material, the above problems have been overcome by coating a hydrophilic polymer having a hydroxyl group and methoxydiethylene glycol group onto the surface. One possible problem with the coated filter material is elution of the hydrophilic polymer. Although the possibility of the polymer elution into an aqueous solution is very low, a material with a smaller risk of elution has been desired for use in

processing of a large amount of blood, such as that used for extracorporeal circulation, to ensure stability of the filter material when it is kept in contact with an aqueous solution such as blood for a long time.

[0007]

JP-A 07-25776 discloses a filter material introduced a polymer having both hydrophobic groups and hydrophilic polyethylene oxide chains by coating. This is a filter material with a reduced risk of polymer elution by decreasing the solubility of the polymer in an aqueous solution by introducing hydrophobic groups into the polymer. However, since the polymer has both hydrophobic groups and hydrophilic groups having opposite properties each other in the polymer molecule, the action of hydrophobic portions through which the polymer is caused to adhere to the supporting body which consists the filter material is reduced. It has, therefore, been difficult to ensure a balance between filter performance and elution properties using this technology alone. The inventors of the present invention examined a polymer having methyl methacrylate and methoxynona(ethylene glycol methacrylate) having polyethylene oxide chains. As a result, the present inventors have found that aqueous solutions become cloudy due to polymer elution.

[0008]

There have been no high performance polymer materials, as the selective leukocyte removal filter, exhibiting both high safety and high blood filtration performance.

[0009]

[Problems to be solved by the invention]

An object of the present invention is to provide selective leukocyte removal filter material which may overcome the problem, which conventional selective leukocyte removal filter materials are easy to elute into a aqueous solution, and can selectively and efficiently remove leukocytes from human whole blood, while controlling the loss of platelet in a small amount.

[0010]

[Means for solving the problems]

As a result of extensive studies for solving the problems described above, the present inventors have found that filter material which has a nonionic polymer comprising a unit originating from a polymerizable monomer having a polyalkylene oxide chain and a unit originating from a hydrophobic polymerizable monomer present on the surface of the filter material surprisingly suppresses the elution remarkably, exhibits both excellent leukocyte removal capability and excellent platelet recovery capability, and is stable even if caused to be in contact with an aqueous solution for a long period of time, when the hydrophobic polymerizable monomer comprises two kinds of a strong hydrophobic polymerizable monomer and a weak hydrophobic polymerizable monomer, and the solubility factor of the polymer and the supporting body having said polymer are limited within a specific range. This finding has led to the completion of the present invention.

[0011]

That is, the present invention provides a selective leukocyte removal filter material for selectively removing leukocytes from blood, which has a nonionic polymer comprising a unit originating from a polymerizable monomer having a

polyalkylene oxide chain and a unit originating from a hydrophobic polymerizable monomer present on the surface of the filter material. The hydrophobic polymerizable monomer comprises two kinds of monomers of a strong hydrophobic polymerizable monomer and a weak hydrophobic polymerizable monomer, and the polymer has a solubility factor (σ value) of not less than 10.0 and not more than 11.5, and the supporting body having said polymer also has σ value of not less than 7.0 and not more than 15.0.

[0012]

It is thought that using the hydrophobic polymerizable monomer comprising two kinds of monomers of a strong hydrophobic polymerizable monomer and a weak hydrophobic polymerizable monomer, although the reason why the extremely high effect of suppressing elution in comparison with the prior arts can be acquired is not clear, the filter material exhibits the effect preventing the adhesion of platelets, hydrophobic proteins together with polyalkylene oxide chain, and at the same time suppresses the elution of the polymer together with the unit originating from a strong hydrophobic polymerizable monomer, as the unit originating from the weak hydrophobic polymerizable monomer has appropriate hydrophilicity and hydrophobicity.

In addition, it is thought that by adding a part having the intermediate property (a weak hydrophobic part) to the part having the contrary properties of hydrophobicity and hydrophilicity, and by the buffering action, the action of the hydrophobic part contacting with the supporting body constituting the filter material may not be weakened, thus sufficient adhesive property is acquired.

[0013]

The polyalkylene oxide chain used in the present invention refers to a repeating structure in which an alkyl group having 2-4 carbon atoms and an oxygen atom bond alternately. The polyalkylene oxide chain includes a polyethylene oxide chain, polypropylene oxide chain, and polybutylene oxide chain, for example. The polyalkylene oxide chain in the polymer exhibits a high platelet adsorption preventing effect due to the outstanding compatibility with blood possessed by the polyalkylene oxide chain. The repeating number of the alkylene oxide chain used in the present invention is preferably from 2 to 10. If the number of repetitions is less than 2, it is difficult to obtain a sufficient platelet adhesion preventing effect. If the number of repetitions is more than 10, the polymer becomes less adhesive to the filter material, thereby increasing a tendency of the polymer eluting more easily. The number of repetitions is preferably 2 to 6, and more preferably 2 to 4.

[0014]

Examples of the polymerizable monomer having the polyalkylene oxide chain include, but are not limited to, methoxydiethylene glycol (meth)acrylate, ethoxydiethylene glycol (meth)acrylate, methoxydipropylene glycol (meth)acrylate, ethoxydipropylene glycol (meth)acrylate, methoxytriethylene glycol (meth)acrylate, methoxytripropylene glycol (meth)acrylate, ethoxytriethylene glycol (meth)acrylate, ethoxytripropylene glycol (meth)acrylate, methoxytetraethylene glycol (meth)acrylate, methoxytetrapropylene glycol (meth)acrylate, ethoxytetraethylene glycol (meth)acrylate,

ethoxytetrapropylene glycol (meth)acrylate, methoxydiethylene glycol vinyl ether, ethoxydiethylene glycol vinyl ether, methoxytriethylene glycol vinyl ether, and ethoxytriethylene glycol vinyl ether. Of these, (meth)acrylate having a polyethylene glycol chain such as methoxydiethylene glycol (meth)acrylate, ethoxydiethylene glycol (meth)acrylate, methoxytriethylene glycol (meth)acrylate, ethoxytriethylene glycol (meth)acrylate, methoxytetraethylene glycol (meth)acrylate, and ethoxytetraethylene glycol (meth)acrylate are preferably used due to the high platelet adsorption preventing effect. Methoxydiethylene glycol (meth)acrylate is most preferable from the viewpoint of easy availability, easy handling, easy polymerization, and the like. The (meth)acrylate in the present invention refers to acrylate and/or methacrylate.

[0015]

It is preferable for the polymer of the present invention to contain the unit originating from the polymerizable monomer having a polyalkylene oxide chain in an amount from 8 mol% to 45 mol%. If less than 8 mol%, the hydrophilicity of the polymer decreases, thus adhesion of platelets to the surface of the filter material may be increased unpreferably. If more than 45 mol%, the hydrophobicity of the polymer decreases, giving rise to easy elution of the polymer when coming into contact with an aqueous solution such as blood. The amount of the unit is preferably from 20 mol% to 40 mol%, and more preferably from 25 mol% to 35 mol%.

[0016]

The term "unit" in the present invention refers to a

minimum recurring unit in a polymer molecule originating from respective polymerizable monomers. For example, in the case of the addition polymerization of a polymerizable monomer of a vinyl compound with the formula CH_2=CXY (wherein X is H or a substituent other than H and Y is a substituent other than X) by simply opening the double bond, the minimum recurring unit is -(CH_2-CXY)-. In the case where the polymer is synthesized by polycondensation from a polymer precursor of the formula A-(R)-B, wherein R indicates a part not released in the polymerization and A and B are releasable parts during the polymerization reaction, -(R)- is the minimum recurring unit.

[0017]

The term "strong hydrophobic polymerizable monomer" in the present invention refers to a polymerizable monomer having solubility in water at 20°C of 0 wt% or more and less than 3 wt%, and not containing a polyalkylene oxide chain in the molecule. The unit originating from a strong hydrophobic polymerizable monomer has effects of decreasing the solubility of the polymer in an aqueous solution, preventing elution of the polymer, and increasing leukocyte removal performance.

[0018]

The solubility can be determined by a known method such as a dew point method, thermal analysis, electric method comprising measurement of the electromotive force or electric conductivity of the solution, gas chromatography analysis, and tracer method in the case where the monomer is a solid. When the monomer is a liquid, the solubility can be determined by, in addition to the methods applied to a solid monomer, a capacitance method, light scattering method, vapor pressure

method, or the like, all of which are known in the art. As a simpler method, when the monomer has a boiling point sufficiently higher than the boiling point of water, a method of vaporizing water from a saturated solution of the monomer and measuring the weight of the residue can be used.

[0019]

As examples of the above-mentioned strong hydrophobic polymerizable monomer, styrene, methylstyrene, butyl (meth)acrylate, isobutyl (meth)acrylate, propyl (meth)acrylate, isopropyl (meth)acrylate, ethyl (meth)acrylate, methyl (meth)acrylate, phenyl (meth)acrylate, ethylhexyl (meth)acrylate, and vinyl acetate can be given. Of these, alkyl (meth)acrylates such as butyl (meth)acrylate, isobutyl (meth)acrylate, propyl (meth)acrylate, isopropyl (meth)acrylate, ethyl (meth)acrylate, and methyl (meth)acrylate are preferably used due to their adequately hydrophobic and easily polymerizable properties. Methyl (meth)acrylate is most preferable from the viewpoint of high biological safety.

[0020]

It is preferable for the polymer of the present invention to contain the unit originating from the strong hydrophobic polymerizable monomer in an amount from 30 mol% to 90 mol%. If less than 30 mol%, the hydrophobicity of the polymer decreases, giving rise to easy elution of the polymer when coming into contact with an aqueous solution such as blood. If more than 90 mol%, the hydrophobicity of the polymer increases, giving rise to increased adsorption of platelets to the surface of the filter material. The amount of the unit is preferably from 35

mol% to 80 mol%, and more preferably from 40 mol% to 70 mol%.

[0021]

The weak hydrophobic polymerizable monomer of the present invention preferably has solubility in water at 20°C in the range from 3 wt% or more, but less than 50 wt%, and is a polymerizable monomer not containing a polyalkylene oxide chain in the molecule. It is thought that the unit originating from a weak hydrophobic polymerizable monomer in the polymer has the appropriate hydrophilic and hydrophobic properties, and thus exhibits the effect of preventing adsorption of platelets and hydrophobic proteins together with the polyalkylene oxide chain, and, at the same time, the effect of preventing elution of the polymer together with a unit originating from strong hydrophobic polymerizable monomers. As the weak hydrophobic polymerizable monomer, a polymerizable monomer having an alkylhydroxyl group such as 2-hydroxypropyl (meth)acrylate, 2-hydroxyisobutyl (meth)acrylate and the like are preferably used due to their appropriate hydrophilic and hydrophobic properties. Of these, 2-hydroxyisobutyl (meth)acrylate is most preferable from the viewpoint of the appropriate hydrophilic properties.

[0022]

The content of the unit originating from weak hydrophobic polymerizable monomer of the present invention in the hydrophobic polymerizable monomer is preferably from 5 to 50 mol%. If the content is less than 5 mol%, the hydrophilicity and hydrophobicity adding effects described above is not sufficient, and the adhesion property of the polymer with the supporting body which consists the filter material may unpreferably decrease. If more than 50 mol%, the hydrophobicity

of the polymer decreases, giving rise to easy elution of the polymer when coming into contact with an aqueous solution such as blood. The content is preferably from 5 to 40 mol%, and more preferably from 10 to 35 mol%.

[0023]

The chemical composition of a polymer can be determined by extracting the polymer using an appropriate solvent which does not dissolve the supporting body of the filter and analyzing the extract by a known method such as NMR spectrum, IR spectrum, and elemental analysis. When the polymer is not dissolved, in addition to the above-mentioned methods, known surface analytical methods such as X-ray photoelectron spectroscopy (ESCA) and a method of using an electron probe X-ray microanalyser (EPMA) can be used.

[0024]

It is necessary for the polymer of the present invention to be nonionic. "Nonionic" means that it does not anionize or cationize in the vicinity of neutral pH of blood, body fluid, or the like, and it does not have a functional group shown minus charge, such as carboxylic acid group, sulfonic acid group, phosphoric acid group, phenol group, or the like, or a functional group shown plus charge, such as primary amino group, secondary amino group, tertiary amino group, quaternary amino group, pyridyl group, imidazoyl group, or the like.

[0025]

The blood clotting factor XII is said to be activated and cause a chain reaction in the clotting system on a negatively charged material surface. A positively charged material surface, on the other hand, tends to adsorb blood cells such

as erythrocytes, platelets, and leukocytes due to the electrostatic interaction with the negative charge on the cell surface. JP-A 06-51060 discloses a technology for removing leukocytes more efficiently while preventing platelet adsorption by providing a slightly positively charged surface. However, electrostatic interaction is not desirable, because high platelet recovery performance is necessary for processing a large amount of blood. s the polymer of the present invention comprises a polymerizable monomer which does not have charge, the clotting system is activated only slightly so that stable platelet recovery performance can be attained even if the polymer is used for large scale blood treatment such as extracorporeal circulation.

[0026]

The polymer of the present invention preferably has a weight average molecular weight (Mw) in the range of 50,000 to 3,000,000. If the Mw is less than 50,000, the molecular weight of the polymer decreases when the polymer is sterilized, particularly by radiation, giving rise to an increase in the eluted amount. If the weight average molecular weight (Mw) is more than 3,000,000, solubility of the polymer in the solvent used for coating decreases. In addition, there may be the case where the polymer cannot be produced in a stable manner. The Mw is more preferably from 100,000 to 2,000,000, and most preferably from 200,000 to 1,500,000. Although the Mw can be determined by various known methods, a value determined by gel permeation chromatography (hereinafter abbreviated to GPC) using polymethyl methacrylate as a standard was used in the present invention.

[0027]

The polymer of the present invention is produced from three components of a polymerizable monomer having a polyalkylene oxide chain, a polymerizable monomer having a strong hydrophobic group and a polymerizable monomer having a weak hydrophobic group, and may be either a random copolymer or a block copolymer. The random copolymer is, however, more preferable since the block copolymer may have a tendency of decreasing the solubility in a solvent when used for coating and may have a tendency of impairing coating uniformity due to micelle formation in the solution. As the form of the polymer molecule chain, a linear polymer is more preferable since a branched polymer may have a tendency of decreasing the solubility in a solvent when used for coating and may have a tendency of impairing coating uniformity due to micelle formation in the solution.

[0028]

A common polymerization method can be employed for synthesizing the polymer of the present invention. Addition polymerization (vinyl polymerization) and the like involving chain reactions; isomerization polymerization; and dissociation reaction, polyaddition, polycondensation, addition polycondensation, and the like involving consecutive reactions may be employed. Radicals, ions, and the like can be used as chain carriers in producing the polymer.

[0029]

As the type of polymerization, solution polymerization, mass polymerization, deposition polymerization, emulsion polymerization, and the like can be given. Of these, solution polymerization is preferable. An example of the polymerization

method is given below. A special grade ethanol solution in which each monomer or a diazo initiator is dissolved is added dropwise to ethanol used as a polymerization solvent while stirring at a constant temperature below the boiling point of ethanol in a nitrogen atmosphere. A stabilizer and the like may be added as appropriate. The reaction yield is measured and confirmed by using a known method such as gas chromatography.

[0030]

The reaction product may be purified by a common chemical purification method to remove impurities such as low molecular weight components and unreacted materials which are contained in the polymer or the reaction solution containing the polymer. As the purification method, a method comprising dissolving the reaction mixture in a solvent that dissolves the impurities, but does not dissolve the polymer, to cause the polymer to precipitate, and separating the precipitate (polymer) by filtration, decantation, or the like can be given. As required, the precipitate is washed with a solvent with solubility slightly higher than that of the precipitation solvent (a mixture of the precipitation solvent and a solvent, for example) and the precipitate is dried under reduced pressure until the weight of the precipitate becomes constant, thereby obtaining a solid polymer.

[0031]

The selective leukocyte removal filter material of the present invention has the polymer at least on the surface of the filter material. The term "has the polymer at least on the surface" indicates the polymer is present on the surface of the supporting body, and substantially coats the surface. As the

method for having the polymer present on the surface of filter, known methods such as a method of coating or depositing and insolubilizing the polymer on the supporting body, a method of phase-separating the polymer from the supporting body during fabrication, and the like can be used. Of these, the method of coating is most preferable due to the easy industrial applicability and excellent performance stability.

[0032]

Since the polymer used for the filter material for removing leukocytes of the present invention comes into contact with body fluids such as blood, it is necessary for the polymer to have extremely low solubility in water. To prevent detachment of the polymer from the supporting body, it is desirable that the polymer has high adsorption with supporting body. As the index for solubility of the polymer in water and adsorption of the polymer with the supporting body, the σ-value of the solubility parameter described in J. H. Hildebrand and R. L. Scott, The Solubility of Nonelectrolytes, 3rd ed. (Dover Pub., New York) can be used. In general, the closer the σ-value of two substances, the stronger the adsorption and the higher the solubility of the two substances. Therefore, the polymer used for the filter material for selectively removing leukocytes of the present invention should preferably have a σ-value that differs largely from the σ-value (23.3) of water and is close to the σ-value of the supporting body. A combination of the polymer having a σ-value in the range from 10.0 to 11.5 and the supporting body having the σ-value of in the range from 7.0 to 15.0 can produce a filter material with extremely low solubility in water without a risk of detachment of the polymer from the supporting body.

A preferable combination is the polymer's σ-value of 10.0 to 10.8 and the supporting body's σ-value of 7.2 to 14.5, and a more preferable combination is the polymer's σ-value of 10.0 to 10.5 and the supporting body's σ-value of 7.5 to 14.0.

[0033]

The σ-values can be calculated according to the following equation (1) which is described in the above document:

$$\sigma = (E/V)^{1/2} \qquad (1)$$

wherein E is cohesive energy (cal mol^{-1}) and V is molar volume ($cm^3\ mol^{-1}$).

The Adhesion Handbook, Second Edition, edited by The Adhesion Society of Japan (THE NIKKAN KOGYO SHIMBUN, LTD.) describes σ-values of solvents and polymers measured heretofore. These values can be used. When the values E and V in the equation (1) are unknown, the σ-values can be calculated from the molecular structure according to the Fedors method described in Kozo Shinoda, Solution and Solubility (Maruzen Co., Ltd).

[0034]

Any material having a σ-value of the above range and not damaging blood cells can be used as the supporting body for the filter material for selectively removing leukocytes of the present invention without specific limitations. As examples of such a material, polyester, polyolefin, polyacrylonitrile, polyamide, polystyrene, polyalkyl (meth)acrylate, polyvinyl chloride, polychloroprene, polyurethane, polyvinyl alcohol, polyvinyl acetate, polysulfone, polyether sulfone, polybutadiene, butadiene-acrylonitrile copolymer, styrene-butadiene copolymer, ethylene-vinyl alcohol copolymer, cellulose diacetate, and ethyl cellulose can be given. Of these,

polyester and polyolefin are preferable, with a particularly preferable organic filter material being polyester.

[0035]

Various methods can be used for coating the polymer onto the supporting body without any specific limitations inasmuch as the surface of the supporting body can be coated with a certain degree of uniformity without unduly clogging the pores in the supporting body. Examples of the method for coating the polymer onto the supporting body include, but are not limited to, a method of impregnating the supporting body with a polymer solution, a method of spraying the polymer solution to the supporting body, and a method of applying or transcribing the polymer solution to the supporting body using a rotogravure roll or the like. Of these methods, the method of impregnating the supporting body with a polymer solution and the method of applying or transcribing the polymer solution to the supporting body using a rotogravure roll are preferable due to the excellent continuous productivity and low cost.

[0036]

Various solvents that do not dissolve the supporting body to a noticeable degree can be used as the solvent to dissolve the polymer in the coating operation without any specific limitations. Examples of such a solvent include, but are not limited to, water and aqueous solutions containing an inorganic salt, alcohols such as methanol, ethanol, propanol, and butanol, ketones such as acetone and methyl ethyl ketone, esters such as methyl acetate and ethyl acetate, hydrocarbons such as benzene and cyclohexane, halogenated hydrocarbons such as chloroform and dichloromethane, sulfur-containing solvents such as

dimethyl sulfoxide, amides such as dimethylformamide and dimethylacetamide, and mixtures of two or more of the above solvents to the extent possible.

[0037]

The concentration of the polymer solution used for coating is preferably 0.001 wt% or more, but less than 10 wt%. If the concentration is less than 0.001 wt%, the amount of the polymer on the surface is too small for the filter material to exhibit sufficient biocompatibility such as properties of preventing platelet adsorption. If the concentration is 10 wt% or more, on the other hand, not only does the solution have too great a viscosity to be handled with ease, but also the surface properties of the medical material may be significantly affected. In addition, such a high concentration is too expensive to be efficiently used. For these reasons, the polymer concentration is more preferably 0.005 wt% or more, but less than 7 wt%, and most preferably 0.01 wt% or more, but less than 5 wt%. The coating amount per the material is preferably 0.001 wt% or more, but less than 10 wt% in weight variation. More preferably, the amount of the polymer is 0.005 wt% or more, but less than 7 wt%, with the amount of 0.01 wt% or more, but less than 5 wt% being most preferable.

[0038]

To dry the polymer solution after coating, a method comprising removing excess solvent by mechanical compression, by gravity, or by injecting gas such as air or nitrogen, and treating the coated material in dry air or under reduced pressure at atmospheric temperature or with heating can be employed. Adsorption of the polymer to the supporting body may be further

increased by a heat treatment after coating the polymer or by post processing of irradiating the coated surface with γ-rays, electron beams, or the like. The coating operation may be carried out either during manufacturing the supporting body or after manufacturing the supporting body.

[0039]

From the viewpoint of frequency of the contact with blood in a liquid phase, it is desirable for the filter material for selectively removing leukocytes of the present invention to have a configuration with a large surface area. For example, fibrous structural materials in the form of a nonwoven fabric, fiber, cotton, yarn, bundle, screen, and fabric; polymer porous materials such as sponge; and other structural materials in the form of beads, gel, and the like can be given. Fabric and nonwoven fabric are particularly preferable in view of adsorptivity of leukocytes and handling easiness as a separating medium. Nonwoven fabric is most preferable due to the capability of providing many contact points with leukocytes.

[0040]

In the case of a fibrous structural material such as nonwoven fabric, the average fiber diameter, which affects the cell adsorption capability, is important. If the fiber diameter is too large, the amount and rate of adsorption of leukocytes decrease; if too small, the amount of platelet adsorption increases. The average fiber diameter of the filter material of the present invention is preferably from 0.5 μm to 50 μm, and more preferably from 1 μm to 40 μm, and most preferably from 2 μm to 35 μm.

[0041]

The average fiber diameter in the present invention is determined as follows. A portion deemed to be substantially homogeneous is sampled from one or more pieces of fabrics forming the filter material and photographed using a scanning electron microscope or the like. For sampling, an effective filtration cross-sectional area of the fabric is divided into squares with one side length of 0.5 cm and six squares are randomly sampled. In random sampling, each divided square is numbered and the required number of squares is selected by using a table of random numbers, for example. Photographs with a magnification of 2,500 are taken at three or more, preferably five or more locations for each sampled square. Photographs for the central parts and the neighborhood areas of each sampled square are taken until the total number of fibers taken in the photographs becomes 100. The diameter herein refers to the width of fiber in the direction perpendicular to the fiber axis. Then, the average diameter is determined by dividing the sum of the diameters of all measured fibers by the number of the fibers. However, the data obtained are excluded, for example, in the cases where multiple fibers overlap precluding diameter measurement of a fiber which hides itself behind another fiber, multiple fibers are consolidated into a fiber with a larger diameter due to fusing or else, or there are fibers with remarkably different diameters.

[0042]

The filter material of the present invention is effectively used for a selective leukocyte removal apparatus filled with the material in a container having at least an inlet port and an outlet port, or an apparatus for extracorporeal circulation for the purpose of removing leukocytes. There are

no specific limitations to the shape of the container inasmuch as the container has an inlet port and an outlet port. Examples of such a container include a container in which the filter material for selectively removing leukocytes can be filled in the form of laminated layers, a cylindrical container, a columnar container such as a triangular prism, a quadratic prism, a hexagonal cylinder, and octagonal cylinder, a container in which the filter material for selectively removing leukocytes rolled in the form of a cylinder can be filled, and a cylindrical container allowing a blood flow to come into the cylinder from the outer perimeter, converging blood into the innermost area, and letting the blood to flow out from an outlet port. Furthermore, a container in which the cross-sectional area decreases from the inlet port toward the outlet port like cone structure is preferably used.

[0043]

The filling density of the filter material for selectively removing leukocytes in the container of the present invention, which refers to the weight of the packed filter material per unit volume of the container, is from 0.05 g/cm^3 to 0.5 g/cm^3. To increase the efficiency of selective removal of leukocytes, while ensuring a smooth flow of blood by preventing clogging of the filter and suppressing a pressure loss increase, the filling density is preferably from 0.075 g/cm^3 to 0.4 g/cm^3, and most preferably from 0.1 g/cm^3 to 0.35 g/cm^3.

[0044]

One kind of the filter material, or two or more kinds of the filter materials with different shapes each other can be used in the filling method of the selective leukocyte removal

filter material of the present invention in a container. For example, plural filter materials having different average fiber diameter may be arranged so that the fiber diameter is gradually small toward outlet direction, or if desired, a pre-filter having an average fiber diameter of not less than 10 μm and not more than 100 μm that remove micro-agglomerates as main objective may be located at inlet side of the filter material. Furthermore, in the actual treatment of products with the blood filter, if desired, a post-filter having an average fiber diameter of not less than 10 μm and not more than 100 μm that prevent non-uniform flow as main objective may be equipped at outlet side of the filter material. In this case, the pre-filter as well as post-filter may be coated with the polymer of the present invention.

[0045]

The selective leukocyte removal filter material of the present invention can be sterilized by a known method such as radiation sterilization, moist heat sterilization, chemical sterilization, gas sterilization, and dry heat sterilization. The filter material together with a filling liquid is preferably sterilized under the condition of the saturated moisture due to the simple priming operation. A more preferable method is radiation sterilization comprising irradiating the filter material with radiation such as γ-ray and electron beams or moist heat sterilization using high pressure steam or the like. Although any liquid not causing deterioration of the polymer can be used as the filling liquid, an aqueous solution which does not adversely affect to the blood components is necessary. Preferably, culture solution such as PBS(-) solution or Hanks

solution, buffer solution, physiologic saline, antioxidant-containing solution, pure water, or the like can be used. Of these, PBS(-) solution, physiologic saline, and pure water are more preferable, and physiologic saline is most preferable.

[0046]

Since the selective leukocyte removal filter material of the present invention exhibits remarkably little elutant, can selectively remove leukocytes from blood, that is, a concentrated erythrocyte preparation, concentrated platelet preparation, platelet poor plasma preparation, peripheral blood, cell floating solutions containing leukocytes and platelets such as lymph and marrow fluid, the filter material can be effectively and safely used as a selective leukocyte removal in blood product and a selective leukocyte removal for extracorporeal circulation. In particular, since the filter material change very small, and is very stable, even if caused to be in contact with an aqueous solution for a long period of time, the filter material can be effectively used for selective leukocyte removal for extracorporeal circulation designed to process a large amount of blood.

[0047]

The present invention is described below by examples, which should not be construed as limiting the present invention.

[Example 1]

(Synthesis of polymer)

One example of the method of synthesizing the polymer used for preparing a selective leukocyte removal filter by coating will be shown. A reaction vessel equipped with a reflux

condenser was charged with ethanol (277 ml). After bubbling nitrogen into ethanol and stirring the mixture at 73°C for one hour, monomers were added dropwise over 120 minutes while maintaining a nitrogen atmosphere. An initiator solution was added dropwise at the same time over 300 minutes. After completion of the addition of the initiator solution, the monomers were polymerized for further two hours. The monomer mixture was a liquid containing 4.8 g (25.5 mmol) of methoxydiethylene glycol methacrylate (MDG), which corresponds to a polymerizable monomer having an alkylene oxide chain, 4.3 g (42.6 mmol) of methylmethacrylate (MMA), which corresponds to a strong hydrophobic polymerizable monomer, and 2.7 g (17.0 mmol) of 2-hydroxyisobutyl methacrylate (HBMA), which corresponds to a weak hydrophobic polymerizable monomer. The molar ratio of charging the monomers was 30 mol% of MDG, 50 mol% of MMA, and 20 mol% of HBMA. An ethanol solution containing 0.034 g of azobisdimethylvaleronitrile (V-65) was used as the initiator solution. The reaction mixture was added dropwise to purified water to cause the polymer to precipitate. The recovered polymer precipitate was cut into pieces and once again put into purified water, followed by stirring for one hour to wash the polymer. Next, the washed polymer was dried under vacuum at 60°C to obtain the target polymer. The composition of the resulting polymer was analyzed from the integral value of NMR measurement, confirming that the composition was almost in agreement with the charged monomer composition. The σ value of the polymer was calculated according to the Fedors method to confirm that the σ value was 10.29. The weight average molecular weight of the polymer measured by GPC was 6.8×10^5.

[0048]

(Preparation of filter material)

A method of preparing the filter material for selectively removing leukocytes will be described below. 1 g of the polymer obtained was dissolved in 100 ml of a mixed solvent of ethanol and purified water (ethanol:water=70:30). A nonwoven fabric made from polyethylene terephthalate was immersed in the solvent. After removing excessive liquid, the nonwoven fabric was dried at room temperature for 16 hours to obtain the target filter. The σ value of the supporting body constituting the filter material was 10.30, the average fiber diameter of the filter material was 2.7 μm, the weight per square meter was 90 g/m^2, and the thickness was 0.42 mm.

[0049]

(Elution test)

The method of the elution test is described as follows. A 200 ml container was packed with 15 g of the filter material as above prepared, a physiological saline solution was filled into the container, and γ-ray sterilization (irradiation dose: 25 kGy) was conducted. To confirm elution in the temperature range possibly occurring during actual preservation of medical devices, the container was allowed to stand at 25°C for 24 hours, then at 4°C for 24 hours. The appearance of the filled solution after preservation was observed to confirm that the solution was transparent and colorless, with no change as compared with the state before sterilization.

[0050]

(Evaluation of blood properties (blood performance test))

Next, a test method for evaluating the leukocyte removal

rate and platelet recovery rate will be described. The filter material prepared in the above was cut into disks, each with a diameter of 6.8 mm. Eight sheets of the disks were laminated in a 1 ml column having an inlet port and an outlet port. The column was filled with a physiological saline solution and sterilized with γ-ray (irradiation dose: 25 kGy) to prepare the column for performance evaluation. 3 ml of fresh human blood (number of leukocytes: 4,500-8,400/μl, number of platelets: 150,000-440,000/μl) to which ACD-A was added as an anti-coagulator (blood:ACD-A=8:1) was fed into the column from the inlet port using a syringe pump at a constant flow rate of 0.5 ml/min. The processed blood was recovered. The leukocyte concentration and platelet concentration in the blood before and after passing through the column were measured using an automatic blood cell counter (Sysmex SF-3000, manufactured by Toa Medical Electronics Co., Ltd.), and the leukocyte removal rate and the platelet recovery rate were calculated by the following equations.

Leukocyte removal rate (%)

= (1-Leukocyte concentration in the outlet port side blood/Leukocyte concentration in the inlet port side blood) x 100

Platelet recovery rate (%)

= (Platelet concentration in the outlet port side blood /Platelet concentration in the inlet port side blood) x 100

As a result, the leukocyte removal rate was 97.5% and the

platelet recovery rate was 85.0%, confirming selective leukocyte removal capability.

[0051]

[Example 2]

A polymer was synthesized in the same manner as in Example 1, except for using 40.0 mol% of MDG, 50.0 mol% of MMA, and 10 mol% of HBMA as the charged monomer composition. The composition of the resulting polymer was analyzed from the integral value of NMR measurement, confirming that the composition was almost in agreement with the charged monomer composition. The σ value of the polymer was calculated according to the Fedors method to confirm that the σ value was 10.04. The weight average molecular weight of the polymer measured by GPC was 8.7×10^5.

A filter material was prepared from the polymer in the same manner as in Example 1. The σ value of the supporting body constituting the filter material was 10.30, the average fiber diameter of the filter material was 2.7 μm, the weight per square meter was 90 g/m^2, and the thickness was 0.42 mm.

Using the obtained filter material, the elution test and the blood performance test were carried out in the same manner as in Example 1. The appearance of the filled solution after sterilization and preservation confirmed that the solution was transparent and colorless, with no change as compared with the state before sterilization. The leukocyte removal rate was 97.0% and the platelet recovery rate was 85.0%, confirming selective leukocyte removal capability.

[0052]

[Example 3]

1 g of the polymer obtained in Example 1 was dissolved in 100 ml of a mixed solvent of ethanol and purified water (ethanol:water=70:30). A nonwoven fabric made from polypropylene was immersed in the solvent. After removing excessive liquid, the nonwoven fabric was dried at room temperature for 16 hours to obtain the target filter material. The σ value of the supporting body constituting the filter material was 7.90, the average fiber diameter of the filter material was 2.6 μm, the weight per square meter was 80 g/m^2, and the thickness was 0.51 mm.

Using the obtained filter material, the elution test was carried out in the same manner as in Example 1. The appearance of the filled solution after sterilization and preservation confirmed that the solution was transparent and colorless, with no change as compared with the state before sterilization.

The filter material prepared in the above was cut into disks, each with a diameter of 6.8 mm. 13 sheets of the disks were laminated in a 1 ml column having an inlet port and an outlet port. The blood performance test was carried out in the same manner as in Example 1. The leukocyte removal rate was 96.5% and the platelet recovery rate 78.0%, confirming selective leukocyte removal capability.

[0053]

[Example 4]

A polymer was synthesized in the same manner as in Example 1, except for using 20 mol% of MDG, 60 mol% of MMA, and 20 mol% of HBMA as the charged monomer composition. The composition of the resulting polymer was analyzed from the integral value of NMR measurement, confirming that the composition was almost

in agreement with the charged monomer composition. The σ value of the polymer was calculated according to the Fedors method to confirm that the σ value was 10.31. The weight average molecular weight of the polymer measured by GPC was 9.2×10^5.

A filter material was prepared from the obtained polymer in the same manner as in Example 3. The σ value of the supporting body constituting the filter material was 7.90, the average fiber diameter of the filter material was 2.6 μm, the weight per square meter was 80 g/m^2, and the thickness was 0.51 mm.

Using the obtained filter material, the elution test and the blood performance test were carried out in the same manner as in Example 1. The appearance of the filled solution after sterilization and preservation confirmed that the solution was transparent and colorless, with no change as compared with the state before sterilization. The leukocyte removal rate was 98.5% and the platelet recovery rate 89.4%, confirming selective leukocyte removal capability.

[0054]

[Example 5]

A polymer was synthesized in the same manner as in Example 1, except for using n-butyl methacrylate (BMA) as a strong hydrophobic polymerizable monomer and 2-hydroxyisopropyl methacrylate (HPMA) as a polymerizable monomer having a weak hydrophobic group, and charging 20 mol% of MDG, 50 mol% of BMA, and 30 mol% of HPMA as the charged monomer composition. The composition of the resulting polymer was analyzed from the integral value of NMR measurement, confirming that the composition was almost in agreement with the charged monomer composition. The σ value of the polymer was calculated

according to the Fedors method to confirm that the σ value was 10.46. The weight average molecular weight of the polymer measured by GPC was 1.1×10^5.

A filter material was prepared from the polymer in the same manner as in Example 1. The σ value of the supporting body constituting the filter material was 10.30, the average fiber diameter of the filter material was 2.7 μm, the weight per square meter was 90 g/m^2, and the thickness was 0.42 mm.

Using the obtained filter material, the elution test and the blood performance test were carried out in the same manner as in Example 1. The appearance of the filled solution after sterilization and preservation confirmed that the solution was transparent and colorless, with no change as compared with the state before sterilization. The leukocyte removal rate was 93.8% and the platelet recovery rate was 83.7%, confirming selective leukocyte removal capability.

[0055]

[Comparative Example 1]

A polymer was synthesized in the same manner as in Example 1, except for using 5.0 mol% of MDG, 5.0 mol% of MMA, and 90.0 mol% of HPMA as the charged monomer composition. The composition of the resulting polymer was analyzed from the integral value of NMR measurement, confirming that the composition was almost in agreement with the charged monomer composition. The σ value of the obtained polymer was calculated according to the Fedors method to confirm that the σ value was 12.39. The weight average molecular weight of the polymer measured by GPC was 3.2×10^5.

A filter material was prepared from the polymer in the

same manner as in Example 1. The σ value of the supporting body constituting the filter material was 10.30, the average fiber diameter of the filter material was 2.7 μm, the weight per square meter was 90 g/m^2, and the thickness was 0.42 mm.

Using the obtained filter material, the elution test and the blood performance test were carried out in the same manner as in Example 1. The filled solution after sterilization and preservation was cloudy, confirming that the polymer eluted during sterilization and preservation. The leukocyte removal rate was 93.3% and the platelet recovery rate 3.1%, confirming a low platelet recovery rate.

[0056]

[Comparative Example 2]

A polymer was synthesized in the same manner as in Example 1, except for using methoxynonaethylene glycol methacrylate (MNG) as a polymerizable monomer having a polyalkylene oxide chain and charging 65.0 mol% of MNG and 35.0 mol% of MMA as the monomer composition. The composition of the resulting polymer was analyzed from the integral value of NMR measurement, confirming that the composition was almost in agreement with the charged monomer composition. The σ value of the polymer was calculated according to the Fedors method to confirm that the σ value was 9.64. The weight average molecular weight of the polymer measured by GPC was 2.2 x 10^5.

A filter material was prepared from the obtained polymer in the same manner as in Example 1. The σ value of the supporting body constituting the filter material was 10.30, the average fiber diameter of the filter material was 2.7 μm, the weight per square meter was 90 g/m^2, and the thickness was 0.42 mm.

Using the obtained filter material, the elution test and the blood performance test were carried out in the same manner as in Example 1. The filled solution after sterilization and preservation was cloudy, confirming that the polymer eluted during sterilization and preservation. The leukocyte removal rate was 99.5% and the platelet recovery rate was 52.0%, confirming a low platelet recovery rate.

[0057]

[Comparative Example 3]

A polymer was synthesized in the same manner as in Example 1, except for charging 100 mol% of methoxyethylene glycol methacrylate (MEGM) as a polymerizable monomer having a alkylene oxide chain. The σ value of the obtained polymer was calculated according to the Fedors method to confirm that the σ value was 9.76. The weight average molecular weight of the polymer measured by GPC was 9.1×10^4.

A filter material was prepared from the obtained polymer in the same manner as in Example 1. The average fiber diameter of the filter material was 2.7 μm, the weight per square meter was 90 g/m^2, and the thickness was 0.42 mm.

Using the obtained filter material, the elution test and the blood performance test were carried out in the same manner as in Example 1. The filled solution after sterilization and preservation was cloudy, confirming that the polymer eluted during sterilization and preservation. The leukocyte removal rate was 98.3% and the platelet recovery rate was 19.1%, confirming a low platelet recovery rate.

[0058]

[Comparative Example 4]

A polymer was synthesized in the same manner as in Example 1, except for using 5.0 mol% of MDG, 50.0 mol% of MMA, and 45.0 mol% of HBMA as the charged monomer composition. The composition of the resulting polymer was analyzed from the integral value of NMR measurement, confirming that the composition was almost in agreement with the charged monomer composition. The σ value of the polymer was calculated according to the Fedors method to confirm that the σ value was 10.89. The weight average molecular weight of the polymer measured by GPC was 1.2×10^5.

1 g of the polymer obtained was dissolved in 100 ml of a mixed solvent of ethanol and purified water (ethanol:water=70:30). A nonwoven fabric made from cellulose was immersed in the solvent. After removing excessive liquid, the nonwoven fabric was dried at room temperature for 16 hours to obtain the target filter. The σ value of the filter supporting body was 15.65, the average fiber diameter of the filter material was 4.1 μm, the weight per square meter was 18 g/m^2, and the thickness was 0.1 mm.

Using the prepared filter material, the elution test was carried out in the same manner as in Example 1. The filled solution after sterilization and preservation was cloudy, confirming that the polymer eluted during sterilization and preservation.

The filter material prepared in the above was cut into disks, each with a diameter of 6.8 mm. 28 sheets of the disks were laminated in a 1 ml column having an inlet port and an outlet port. The blood performance test was carried out in the same manner as in Example 1. The leukocyte removal rate was 85.1%

and the platelet recovery rate 45.4%, confirming rather low recovery rate of platelets.

[0059]

The results are summarized in Table 1.

[Table 1]

	Example					Comparative Example			
	1	2	3	4	5	1	2	3	4
Polymerizable monomer having polyalkylene oxide chain (mol %)	30	40	30	20	20	5	35	100	5
Polymerizable monomer having a hydrophobic group (mol %) A	50	50	50	60	50	5	65	0	50
Polymerizable monomer having hydroxyl group (mol %) B	20	10	20	20	30	90	0	0	45
B x 100/(A+B) (mol %)	28.6	16.7	28.6	25.0	37.5	94.7	0	0	47.4
σ-Value of polymer	10.29	10.04	10.29	10.31	10.46	12.39	9.64	9.76	10.87
σ-Value of filter supporting body	10.30	10.30	7.90	7.90	10.30	10.30	10.30	10.30	15.62
Elution test: Filling solution appearance	Tp*	Tp	Tp	Tp	Tp	Cl	Cl	Cl	Cl
Blood performance test:									
Leukocyte removal rate (%)	97.5	97.0	96.5	98.5	93.8	93.3	99.5	98.3	85.1
Platelet recovery rate (%)	85.0	85.0	78.0	89.4	83.7	3.1	52.0	19.1	45.4

* Tp: Transparent and colorless, Cl: Cloudy

As can be seen from Table 1, the filter materials having a nonionic polymer comprising a unit originating from a polymerizable monomer having a polyalkylene oxide chain, and a unit originating from a hydrophobic polymerizable monomer, on the surface of the filter material, and further the filter materials having two kinds of hydrophobic polymerizable monomers comprising a strong hydrophobic polymerizable monomer and a weak hydrophobic polymerizable monomer, and having both σ values of the polymer and the supporting body holding the

polymer within specific region were confirmed to elute only a minimal amount of polymer components and to exhibit selective leukocyte removal capability. On the other hand, the filter materials not meeting these conditions did not satisfy both the elution test and the blood performance test.

[0060]

[Effects of the invention]

The selective leukocyte removal filter material of the present invention can overcome the problem that conventional selective leukocyte removal filter materials are easy to elute into an aqueous solution, and can selectively and efficiently remove leukocytes, while controlling the loss of platelets from blood in a small amount. Therefore, the selective leukocyte removal filter material can be used as the selective leukocyte removal apparatus for preparing blood product or for extracorporeal circulation by filling with the material in a container having at least an inlet port and an outlet port.

[Document Name] Abstract

[Abstract]

[Problems] The present invention is to provide a elective leukocyte removal filter material which does not elute into an aqueous solution with difficulty, and can selectively and effectively remove leukocytes, while controlling the loss of platelets in a small amount from human whole blood.

[Means for solving] A selective leukocyte removal filter material for selectively removing leukocytes, which has a polymer present at least on the surface of the supporting body, wherein the polymer is a nonionic polymer which comprises a unit originating from a polymerizable monomer having a polyalkylene oxide chain and a unit originating from a hydrophobic polymerizable monomer comprising both a strong hydrophobic polymerizable monomer and a weak hydrophobic polymerizable monomer, and the polymer has 10.0 - 11.5 of solubility factor (σ value) and the supporting body having the above polymer has 7.0 - 15.0 of σ value. Therefore, the above problems can be dissolved.

[Drawing] None

Solubility Parameters: Theory and Application

John Burke
The Oakland Museum of California
August 1984
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Solvents are ubiquitous: we depend on them when we apply pastes and coatings, remove stains or old adhesives, and consolidate flaking media. The solubility behavior of an unknown substance often gives us a clue to its identification, and the change in solubility of a known material can provide essential information about its ageing characteristics.

Our choice of solvent in a particular situation involves many factors, including evaporation rate, solution viscosity, or environmental and health concerns, and often the effectiveness of a solvent depends on its ability to adequately dissolve one material while leaving other materials unaffected. The selection of solvents or solvent blends to satisfy such criterion is a fine art, based on experience, trial and error, and intuition guided by such rules of thumb as "like dissolves like" and various definitions of solvent "strength". While seat-of-the-pants methods are suitable in many situations, any dependence on experiential reasoning at the expense of scientific method has practical limitations. Although it may not be necessary to understand quantum mechanics to remove masking tape, an organized system is often needed that can facilitate the accurate prediction of complex solubility behavior.

SOLUBILITY SCALES

Product literature and technical reports present a bewildering assortment of such systems: Kauri-Butanol number, solubility grade, aromatic character, aniline cloud point, wax number, heptane number, and Hildebrand solubility parameter, among others. In addition, the Hildebrand solubility parameter, perhaps the most widely applicable of all the systems, includes such variations as the Hildebrand number,

hydrogen bonding value, Hansen parameter, and fractional parameter, to name a few. Sometimes only numerical values for these terms are encountered, while at other times values are presented in the form of two or three dimensional graphs, and a triangular graph called a Teas graph has found increasing use because of its accuracy and clarity.

Understandably, all this can be slightly confusing to the uninitiated. Graphic plots of solvent-polymer interactions allow the fairly precise prediction of solubility behavior, enabling the control of numerous properties in practical applications that would be very difficult without such an organizing system. Yet the underlying theories are often extremely complex, and an understanding of the "why" of a particular system can be very difficult, enough to discourage the use of such systems. Many of the systems mentioned, however, are actually quite simple (this is especially true of the Teas graph) and can be used to advantage with little understanding of the chemical principles at work.

This paper will attempt to bridge these two realities by briefly introducing solubility theory as well as its application so that the conservator will be both better able to understand and profitably apply the concepts involved. The discussion will center on Hildebrand solubility parameters and, after laying a theoretical foundation, will concentrate on graphic plots of solubility behavior. It should be remembered that these systems relate to non-ionic liquid interactions that are extended to polymer interactions; water based systems and those systems involving acid-base reactions cannot be evaluated by simple solubility parameter systems alone.

Solutions and Molecules

A **solvent**, usually thought of as a liquid, is a substance that is capable of dissolving other substances and forming a uniform mixture called a **solution**. The substance dissolved is called the **solute** and is usually considered to be the component present in the smallest amount. According to this definition, an almost-dry or slightly swollen resin film comprises a solution of a liquid (the solute) in a resin (the solvent), even though conventionally the liquid is usually referred to as the solvent, and the resin as the solute.

MOLECULAR ATTRACTIONS

Liquids (and solids) differ from gases in that the molecules of the liquid (or solid) are held together by a certain amount of intermolecular stickiness. For a solution to occur, the solvent molecules must overcome this intermolecular stickiness in the solute and find their way between and around the solute molecules. At the same time, the solvent molecules themselves must be separated from each other by the molecules of the solute. This is accomplished best when the attractions between the molecules of both components are similar. If the attractions are sufficiently different, the strongly attracted molecules will cling together, excluding the weakly attracted molecules, and **immiscibility** (not able to be mixed) will result. Oil and water do not mix because the water molecules, strongly attracted to each other, will not allow the weakly attracted oil molecules between them.

VAN DER WAALS FORCES

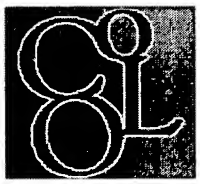
These sticky forces between molecules are called **van der Waals forces** (after Johannes van der Waals who first described them in 1873). Originally thought to be small gravitational attractions, Van der Waals forces are actually due to electromagnetic interactions between molecules.

The outer shell of a neutral atom or molecule is composed entirely of negatively charged electrons, completely enclosing the positively charged nucleus within. Deviations in the electron shell density, however, will result in a minute magnetic imbalance, so that the molecule as a whole becomes a small magnet, or **dipole**. These electron density deviations depend on the physical architecture of the molecule: certain molecular geometries will be strongly **polar**, while other configurations will result in only a weak polarity. These differences in polarity are directly responsible for the different degrees of intermolecular stickiness from one substance to another. Substances that have similar polarities will be soluble in each other but increasing deviations in polarity will make solubility increasingly difficult.

Van der Waals forces, then, are the result of intermolecular polarities. As we shall see, accurate predictions of solubility behavior will depend not only on determining the *degree* of intermolecular attractions between molecules, but in discriminating between different *types* of polarities as well. A single molecule, because of its structure, may exhibit van der Waals forces that are the additive result of two or three different kinds of polar contributions. Substances will dissolve in each other not only if their intermolecular forces are similar, but particularly if their composite forces are made up in the same way. (Such types of **component** interactions include hydrogen bonds, induction and orientation effects, and dispersion forces, which will be discussed later.)

Next: Part 2 - The Hildebrand Solubility Parameter

[top] [next]



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Solubility Parameters: Theory and Application

John Burke
The Oakland Museum of California
August 1984

Part 2 – The Hildebrand Solubility Parameter

It is the *total* van der Waals force, however, which is reflected in the simplest solubility value: the Hildebrand solubility parameter. The solubility parameter is a numerical value that indicates the relative solvency behavior of a specific solvent. It is derived from the **cohesive energy density** of the solvent, which in turn is derived from the **heat of vaporization**. What this means will be clarified when we understand the relationship between vaporization, van der Waals forces, and solubility.

VAPORIZATION

When a liquid is heated to its boiling point, energy (in the form of heat) is added to the liquid, resulting in an increase in the temperature of the liquid. Once the liquid reaches its boiling point, however, the further addition of heat does not cause a further increase in temperature. The energy that is added is entirely used to separate the molecules of the liquid and boil them away into a gas. Only when the liquid has been completely vaporized will the temperature of the system again begin to rise. If we measure the *amount* of energy (in calories) that was added from the onset of boiling to the point when all the liquid has boiled away, we will have a direct indication of the amount of energy required to separate the liquid into a gas, and thus the amount of van der Waals forces that held the molecules of the liquid together.

It is important to note that we are not interested here with the *temperature* at which the liquid begins to boil, but the *amount of heat* that has to be added to separate the molecules. A liquid with a low boiling point may require considerable energy to vaporize, while a liquid with a higher boiling point may vaporize quite readily, or vise versa. What is important is the energy required to vaporize the liquid, called the **heat of vaporization**. (Regardless of the temperature at which boiling begins, the liquid that vaporizes readily has less intermolecular stickiness than the liquid that requires considerable addition of heat to vaporize.)

COHESIVE ENERGY DENSITY

From the heat of vaporization, in calories per cubic centimeter of liquid, we can derive the **cohesive energy density** (c) by the following expression

$$c = \frac{\Delta H - RT}{V_m} \qquad (1)$$

where:

c=Cohesive energy density
Δh=Heat of vaporization
r=Gas constant
t=Temperature
v_m=Molar volume

In other words, the cohesive energy density of a liquid is a numerical value that indicates the energy of vaporization in calories per cubic centimeter, and is a direct reflection of the degree of van der Waals forces holding the molecules of the liquid together.

Interestingly, this correlation between vaporization and van der Waals forces also translates into a correlation between vaporization and solubility behavior. This is because the same intermolecular attractive forces have to be overcome to vaporize a liquid as to dissolve it. This can be understood by considering what happens when two liquids are mixed: the molecules of each liquid are physically separated by the molecules of the other liquid, similar to the separations that happen during vaporization. The same intermolecular van der Waals forces must be overcome in both cases.

Since the solubility of two materials is only possible when their intermolecular attractive forces are similar, one might also expect that materials with similar cohesive energy density values would be miscible. This is in fact what happens.

SOLUBILITY PARAMETER

In 1936 Joel H. Hildebrand (who laid the foundation for solubility theory in his classic work on the solubility of nonelectrolytes in 1916) proposed the square root of the cohesive energy density as a numerical value indicating the solvency behavior of a specific solvent.

$$\delta = \sqrt{c} = \left[\frac{\Delta H - RT}{V_m}\right]^{1/2} \qquad (2)$$

It was not until the third edition of his book in 1950 that the term "**solubility parameter**" was proposed for this value and the quantity represented by a delta (δ). Subsequent authors have proposed that the term **hildebrands** be adopted for solubility parameter units, in order to recognize the tremendous contribution that Dr. Hildebrand has made to solubility theory.

UNITS OF MEASUREMENT

Table 1 lists several solvents in order of increasing Hildebrand parameter. Values are shown in both the common form which is derived from cohesive energy densities in calories/cc, and a newer form which, conforming to standard international units (SI units), is derived from cohesive pressures. The SI unit for expressing pressure is the pascal, and SI Hildebrand solubility parameters are expressed in mega-pascals (1 mega-pascal or mpa=1 million pascals). Conveniently, SI parameters are about twice the value of standard parameters:

$\delta/cal^{1/2}cm^{-3/2} = 0.48888 \times \delta/MPa^{1/2}$ (3)

$\delta/MPa^{1/2} = 2.0455 \times \delta/cal^{1/2}cm^{-3/2}$ (4)

Literature published prior to 1984 should contain only the common form, designated δ, and it is hoped that where the newer SI units are used, they are designated as such, namely $\delta/MPa^{1/2}$ or δ(SI). Obviously, one must be careful to determine which system of measurement is being used, since both forms are called Hildebrand parameters. This paper will primarily use the SI values, and the use of standard values will be noted.

Table 1

Hildebrand Solubility Parameters
Standard Hildebrand values from Hansen, *Journal of Paint Technology* Vol. 39, No. 505, Feb 1967
SI Hildebrand values from Barton, *Handbook of Solubility Parameters*, CRC Press, 1983
Values in parenthesis from Crowley, et al., *Journal of Paint Technology* Vol. 38, No. 496, May 1966

Solvent	δ	δ(SI)
n-Pentane	(7.0)	14.4
n-Hexane	7.24	14.9
Freon® TF	7.25	
n-Heptane	(7.4)	15.3
Diethyl ether	7.62	15.4
1,1,1 Trichloroethane	8.57	15.8
n-Dodecane		16.0
White spirit		16.1
Turpentine		16.6
Cyclohexane	8.18	16.8
Amyl acetate	(8.5)	17.1
Carbon tetrachloride	8.65	18.0
Xylene	8.85	18.2
Ethyl acetate	9.10	18.2
Toluene	8.91	18.3
Tetrahydrofuran	9.52	18.5
Benzene	9.15	18.7
Chloroform	9.21	18.7
Trichloroethylene	9.28	18.7
Cellosolve® acetate	9.60	19.1

Methyl ethyl ketone	9.27	19.3
Acetone	9.77	19.7
Diacetone alcohol	10.18	20.0
Ethylene dichloride	9.76	20.2
Methylene chloride	9.93	20.2
Butyl Cellosolve®	10.24	20.2
Pyridine	10.61	21.7
Cellosolve®	11.88	21.9
Morpholine	10.52	22.1
Dimethylformamide	12.14	24.7
n-Propyl alcohol	11.97	24.9
Ethyl alcohol	12.92	26.2
Dimethyl sulphoxide	12.93	26.4
n-Butyl alcohol	11.30	28.7
Methyl alcohol	14.28	29.7
Propylene glycol	14.80	30.7
Ethylene glycol	16.30	34.9
Glycerol	21.10	36.2
Water	23.5	48.0

SOLVENT SPECTRUM

In looking over Table 1, it is readily apparent that by ranking solvents according to solubility parameter a solvent "spectrum" is obtained, with solvents occupying positions in proximity to other solvents of comparable "strength". If, for example, acetone dissolves a particular material, then one might expect the material to be soluble in neighboring solvents, like diacetone alcohol or methyl ethyl ketone, since these solvents have similar internal energies. It may not be possible to achieve solutions in solvents further from acetone on the chart, such as ethyl alcohol or cyclohexane—liquids with internal energies very different from acetone. Theoretically, there will be a contiguous group of solvents that will dissolve a particular material, while the rest of the solvents in the spectrum will not. Some materials will dissolve in a large range of solvents, while other might be soluble in only a few. A material that cannot be dissolved at all, such as a crosslinked three-dimensional polymer, would exhibit swelling behavior in precisely the same way.

SOLVENT MIXTURES

It is an interesting aspect of the Hildebrand solvent spectrum that the Hildebrand value of a solvent mixture can be determined by averaging the Hildebrand values of the individual solvents by volume. For example, a mixture of two parts toluene and one part acetone will have a Hildebrand value of 18.7 (18.3 x 2/3 + 19.7 x 1/3),

about the same as chloroform. Theoretically, such a 2:1 toluene/acetone mixture should have solubility behavior similar to chloroform. If, for example, a resin was soluble in one, it would probably be soluble in the other. What is attractive about this system is that it attempts to predict the properties of a mixture *a priori* using only the properties of its components (given the solubility parameters of the polymer and the liquids); no information on the mixture is required.

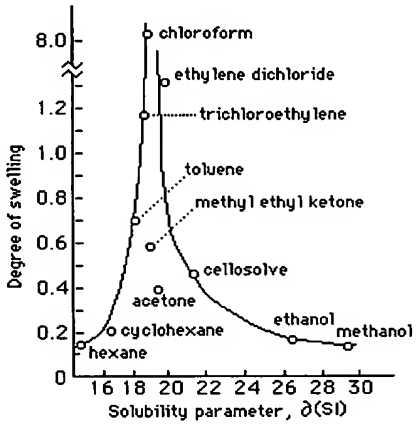

Fig. 1 Swelling of Linseed Oil Film in Solvents Arranged According to Solubility Parameter (adapted from Feller, Stolow, and Jones, *On Picture Varnishes and Their Solvents*)

POLYMER COHESION PARAMETERS

Figure 1 plots the swelling behavior of a dried linseed oil film in various solvents arranged according to Hildebrand number. Of the solvents listed, chloroform swells the film to the greatest degree, about six times as much as ethylene dichloride, and over ten times as much as toluene. Solvents with greater differences in Hildebrand value have less swelling effect, and the range of peak swelling occupies less than two hildebrand units. By extension, we would expect any solvent or solvent mixture with a Hildebrand value between 19 and 20 to severely swell a linseed oil film. (The careful observer will notice certain inconsistencies in Fig. 1 which will be discussed later.)

Since a polymer would decompose before its heat of vaporization could be measured, swelling behavior is one of the ways that Hildebrand values are assigned to polymers (the general term **cohesion parameter** is often preferred to the term solubility parameter when referring to non-liquid materials). Another method involves **cloud-point** determinations in which a resin is dissolved in a true solvent and titrated with another solvent until the mixture becomes cloudy, thus identifying the range of solubility. Testing cloud-points with a variety of solvents and diluents enable a precise determination of cohesion parameter values for polymers. Other methods include a combination of empirical tests, such as cloud-point and solubility/swelling tests, with the addition of theoretical calculations based on comparing chemical structure to other materials of known Hildebrand value.

Next: Part 3 – Other Practical Solubility Scales

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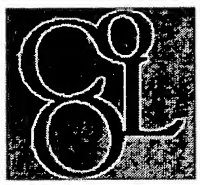

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Solubility Parameters: Theory and Application

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The Oakland Museum of California
August 1984

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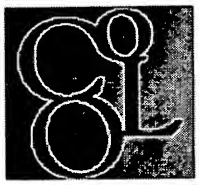

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A Method for Estimating Both the Solubility Parameters and Molar Volumes of Liquids

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The solubility parameters and molar volumes of substances can be used, in conjunction with suitable theory, to provide estimates of the thermodynamic properties of solutions; the solubility characteristics of polymer-solvent systems and the estimation of the equilibrium uptake of liquids by polymers are examples of the type of practical problems that are amenable to treatment.

For low molecular weight liquids, the solubility parameter, δ, is conveniently calculated using the expression $\delta = (\Delta E_v/V)^{1/2}$, where ΔE_v is the energy of vaporization at a given temperature and V is the corresponding molar volume which is calculated from the known values of molecular weight and density.

For high molecular weight polymers, the volatility is much too low for ΔE_v to be obtained directly and hence recourse must be made to indirect methods for estimating δ for these materials. One such widely used method is based on Small's additive group "molar-attraction constants" which when summed allow the estimation of δ from a knowledge of the structural formula of the material; however, the density must still be determined experimentally.

The proposed method of estimating δ, also based on group additive constants is believed to be superior to Small's method for two reasons: 1) the contribution of a much larger number of functional groups have been evaluated, and 2) the method requires only a knowledge of the structural formula of the compound.

INTRODUCTION

The solubility parameter of a liquid, δ, defined as the square root of the cohesive energy density is a quantity which, in conjunction with suitable theory, allows one to estimate several thermodynamic properties of solutions. The cohesive energy density itself is defined as the ratio of the energy of vaporization, ΔE_v, to the molar volume both referred to the same temperature.

The concept of the solubility parameter was developed by Scatchard (1) and subsequently greatly extended by Hildebrand (2) and had as its origin the attempt to formulate an expression for the partial molar energy of mixing, or for the special case of zero volume change, for the heat of mixing of two liquids. The theory has been particularly successful in describing, at least semi-quantitatively, the thermodynamic properties of dilute solutions and especially so when the component liquids are non-polar.

In addition to its importance in the theory of solutions, the solubility parameter or the closely related cohesive energy density has been shown to be connected to other physical properties such as surface tension (3) and wettability (4, 5), the ratio of the coefficient of thermal expansion to compressibility (2), the boiling points in the case of non-polar liquids (2), the ultimate strength of materials (6), and the glass transition temperature of polymers (7) to cite a few examples. Hence, it should be apparent that the ability to estimate the solubility parameter of a liquid can often be an extremely useful tool, applicable to the solution of a diverse number of practical problems.*

An appreciation of the meaning of the solubility parameter in physical terms can be obtained from a study of *Fig. 1*. Parts A and B of the figure depict, in a schematic fashion, the general dependence of

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* A reviewer has pointed out that estimates of the physical properties of a system calculated on the basis of a single solubility parameter can sometimes lead to erroneous conclusions. More satisfactory results can often times be obtained using the three-dimensional solubility parameter approach as developed by Hansen (C. M. Hansen, *Ind. Eng. Chem. Prod. Res. Dev.*, 8, 2 (1968)) in which the solubility parameter, as for example estimated by the method described in this paper, is decomposed into a dispersion, polar and hydrogen bonding contribution. However, this approach requires the availability of experimental data. In the absence of such data, the total solubility parameter as well as molar volume can be estimated from a knowledge of the chemical structure alone using the method described in this paper.

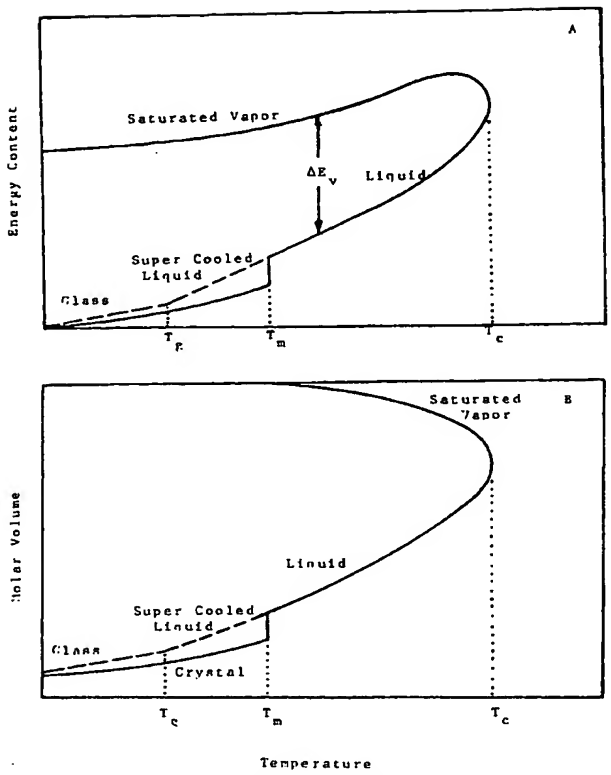


Fig. 1. Dependence of energy content (A) and molar volume (B) on temperature.

both the energy content and molar volume of a substance respectively on the temperature. By definition, the energy of vaporization is the difference between the energy content of the saturated vapor and the energy content of the liquid, both at the same temperature, which in the figure can be conveniently represented by a vertical bar as shown. Also apparent is the fact that ΔE_v is in general a monotonically decreasing function of temperature which eventually takes on the value zero as the critical temperature, T_c, is reached; at this point the properties of the saturated vapor and liquid become identical. The molar volume, on the other hand is seen to be a monotonically increasing function of the temperature. Since the cohesive energy density is the ratio of ΔE_v and V, it is at once apparent that the cohesive energy density as well as the solubility parameter must be a monotonically decreasing function of temperature such that the ratio has a maximum (but hypothetical) value at 0°K and a value of zero at T_c.

The discontinuity apparent in both figures represents the isothermal change in both the energy content and the molar volume as the substance undergoes a crystalline-liquid phase change at the melting temperature, T_m. The difference between the energy content of the vapor and that of the crystalline phase is defined as the energy of sublimation; this quantity too is a decreasing function of temperature. The dashed curves represent the behavior of the supercooled liquid which at a temperature called the glass transition temperature, T_g, transforms into a glass. At T_g, there is a relatively small but abrupt change in the slope in both the energy and volume curves. When estimates are made of either the energy of vaporization or the molar volume using any of the several methods to be described below, for a substance which is crystalline rather than liquid at the temperature in question, then these estimates will represent the difference between the property of the vapor and that of the supercooled liquid.

The cohesive energy density has been discussed in terms of ΔE_v; experimentally, however, it turns out to be more convenient to measure the heat of vaporization, ΔH_v. The connection between these two quantities is simply $\Delta E_v = \Delta H_v - RT$ where R is the gas constant in the appropriate units and T is the absolute temperature.

METHODS FOR ESTIMATING SOLUBILITY PARAMETER

Liquids

For low molecular weight liquids, the solubility parameter at a given temperature is given by

$$\delta = \left(\frac{\Delta H_v}{V} - \frac{RT}{V}\right)^{1/2} = \left(\frac{\Delta E_v}{V}\right)^{1/2} \qquad (1)$$

Values of ΔH_v for use in *Eq 1* are commonly obtained using vapor pressure-temperature data or from heat capacity-temperature measurements. Numerical values for ΔH_v for a diverse number of liquids are available (8, 9).

When values of ΔH_v are known at one temperature, e.g., at the normal boiling point, these can be converted to the appropriate ΔH_v values at any other temperature using the following empirical relationship first proposed by Watson (10):

$$\frac{\Delta H_{v,T_2}}{\Delta H_{v,T_1}} = \left(\frac{T_c - T_2}{T_c - T_1}\right)^{0.38} \qquad (2)$$

This is a remarkable and extremely useful expression since for many liquids values of ΔH_v corresponding only to the normal boiling point have been reported. Furthermore, the expression is surprisingly accurate since the predicted ΔH_v values are generally within about 2 percent of the values obtained experimentally; this is true even for temperatures to within a few degrees of T_c (11). In those instances where T_c for a particular substance is unknown, its value may often be estimated using Lydersen's additive atomic and group contributions (12) provided that the normal boiling temperature is also known or can be estimated (13).

Another convenient and useful method, due to Hildebrand (2), is based on an empirical relationship which relates ΔH_v at 25°C to the normal boiling point, T_b, of non-polar liquids, *viz.*,

$$\Delta H_v = T_b^2 + 23.7T_b - 2950 \qquad (3)$$

This expression can be very useful for estimating ΔH_v since the normal boiling point for many liquids is commonly available in the literature.

Various other methods for estimating heats of vaporization have been reported in the literature; these are fully discussed in several reviews (11-14). In addition, several compilations of solubility parameter values for various liquids are also available (15-19).

Polymers

For amorphous high molecular weight polymers none of the methods described above are directly applicable. Although properly classified as liquids, these materials have a vapor pressure which is too low to detect, hence, information concerning the energy content of the vapor, as shown in *Fig. 1*, is not available. Then too, both T_b and T_c are generally unknown and hence the indirect methods described above which rely on the availability of numerical values for these two parameters are also not applicable.

It is for these reasons that indirect methods must be used and these can be based on various kinds of measurements such as the determination of solubility relationships, of thermal changes accompanying mixing, and of various colligative properties such as vapor pressure, depression of the freezing point, and osmotic pressure; these measurements in conjunction with suitable theory can be used to evaluate δ for polymers.

Specifically, some of the more widely used methods include:

1) Determination of the equilibrium swelling of a crosslinked polymer in a variety of solvents which have a wide range of δ values; the extent of swelling will be a maximum when the δ value of the solvent matches that of the polymer (20).

2) The intrinsic viscosity of the uncrosslinked polymer is measured in a series of solvents and the δ value for the polymer is taken to be the same as that of the solvent in which the polymer has the greatest viscosity (18). A review of these and other methods are discussed in references 18 and 19.

Although these indirect methods are useful, it is true that they are also tedious and time consuming and hence, a great deal of effort has been expended on discovering alternative ways of estimating δ. One of the simplest is based on the assumption that atomic and group increments exist which could be summed over the known structure of the substance (liquids as well as high molecular weight polymers), to provide estimates for δ. Several such systems have been proposed and for both practical and historical interest, the best known will be briefly discussed in turn.

Summation of Atomic and Group Contributions

Dunkel. The first demonstration that the heat of vaporization of liquids, at a given temperature, could be estimated by the summation of atomic and group contributions was apparently provided by Dunkel (21). He showed that ΔH_v could be represented by an equation of the form,

$$\Delta H_v = \sum_i \Delta h_i \qquad (4)$$

where Δh_i is the contribution of the i-th atom or group to the molar heat of vaporization. In general, it can be expected that Δh_i will be a function of temperature because ΔH_v itself is temperature dependent. *Table 1* lists the values of Δh_i reported by Dunkel for various atoms and groups. Hayes (7) has reported values of Δh_i for additional groups not listed in *Table 1;* however, these values are not entirely consistent with those of Dunkel and therefore have not been included.

By substituting *Eq 4* for the appropriate quantities in *Eq 1*, the solubility parameter may be expressed as

$$\delta = \left[\frac{\sum_i \Delta h_i}{V} - \frac{RT}{V} \right]^{1/2} \qquad (5)$$

which can be used to estimate δ for a liquid from a knowledge of the chemical structure provided the appropriate density is known.

When the liquid is a high molecular weight polymer, or an n-mer containing n repeating units, the molar heat of vaporization can be expressed as

$$\Delta H_v = 2\Delta h_{ie} + n\Delta h_{ir} \qquad (6)$$

where Δh_{ie} and Δh_{ir} are the contributions of the end groups and repeating units respectively to the molar heat of vaporization. The heat of vaporization per gram of polymer is obtained by dividing ΔH_v by the molecular weight, M, which itself can be expressed as $M = 2M_e + nM_r$ where M_e is the molecular weight of the end group and M_r the molecular weight of the repeating unit. Hence, *Eq 6* becomes

$$\frac{\Delta H_v}{M} = \frac{2\Delta h_{ie}}{M} + \frac{n\,\Delta h_{ir}}{2M_e + nM_r} \qquad (7)$$

When M is large, the term $2\Delta h_{ie}/M$ approaches zero, and $2M_e$ becomes negligible compared to the term nM_r whereupon *Eq 7* becomes

$$\frac{\Delta H_v}{M} = \frac{\Delta h_{ir}}{M_r} \qquad (8)$$

In addition, since the density ρ is given by the ratio M/V, this expression reduces to

Table 1. Atomic and Group Contributions to the Heat of Vaporization (21)

Atom or group	Δh_i, cal/mole	Atom or group	Δh_i, cal/mole
CH_3	1780	COOH	8970
$=CH_2$	1780	$COOCH_3$	5600
CH_2	990	$COOC_2H_5$	6230
$=CH$	990	NH_2	3530
CH	−380	Cl	3400
O	1630	F*	2060
OH	7250	Br*	4300
$=CO$	4270	I*	5040
CHO	4700	NO_2*	7200
		SH*	4250

* Provisional values.

$$\frac{\Delta H_v}{V} = \rho \frac{\Delta h_{ir}}{M_r} \qquad (9)$$

Substituting *Eq 9* in *Eq 5* the solubility parameter becomes simply

$$\delta = \left(\rho \frac{\Delta h_{ir}}{M_r}\right)^{1/2} \qquad (10)$$

since the second term on the right hand side of *Eq 5* becomes negligible for large V (high molecular weight). *Equation 10* thus represents the asymptote which is approached in the limit of high molecular weight.

Bowden and Jones. These workers showed that for a wide variety of both polar and non polar liquids, the following relationships for both ΔH_v and ΔE_v were closely followed over a wide range of temperature,

$$\frac{M}{(\rho_L - \rho_v)}\left(\frac{\Delta H_v}{M}\right)^{4/5} = [L] \qquad (11)$$

and

$$\frac{M}{(\rho_L - \rho_v)}\left(\frac{\Delta E_v}{M}\right)^{3/4} = [\Lambda] \qquad (12)$$

where ρ_L and ρ_v are the densities of the liquid and vapor respectively and $[L]$ and $[\Lambda]$, which they termed the normal and true lyoparachor respectively, are constants independent of temperature. The exponents were determined empirically from the fit of data to these expressions. For temperatures at or below the normal boiling point of the liquid, the density of the vapor is negligible compared to that of the liquid and *Eqs 11* and *12* can be written simply as,

$$\Delta H_v = M\left(\frac{[L]}{V}\right)^{5/4} \qquad (13)$$

and

$$\Delta E_v = M\left(\frac{[\Lambda]}{V}\right)^{4/3} \qquad (14)$$

Interestingly enough, they found that both the normal and true lyoparachor could be obtained by the summation of atomic and group increments, i.e.,

$$[L] = \sum_i \Delta l_i \qquad (15)$$

and

$$[\Lambda] = \sum_i \Delta\lambda_i \qquad (16)$$

where Δl_i and $\Delta\lambda_i$ are the atomic and group increments listed in *Table 2*. As was the case with the increments derived by Dunkel, the lyoparachor increments permit one to estimate the solubility parameter from a knowledge of the chemical structure of the liquid provided the density is known. Furthermore, *Eq 14* permits one also to estimate the temperature dependence of δ provided the temperature dependence of the density is known.

Using *Eq 16*, the solubility parameter of a liquid can be expressed as

$$\delta = \rho^{5/6}\left[\frac{\sum_i \Delta\lambda_i}{M}\right]^{2/3} \qquad (17)$$

Table 2. Atomic and Group Contributions to the Normal and True Lyoparachor (22)

Atom or group	Δl_i, $\left(\frac{cal}{g}\right)^{\frac{4}{5}} \frac{cm^3}{mole}$	$\Delta\lambda_i$, $\left(\frac{cal}{g}\right)^{\frac{3}{4}} \frac{cm^3}{mole}$
C	−1193.6	−804.5
H	844.8	593.4
N	−112.7	−48.3
O (ether)	178.3	146.5
O (ketone)	2092.1	1505.4
O (ketone)*	2206.0	1573.0
O (carboxylate)	903.6	649.1
O (anhydride)*	1330.5	956.0
O (carbonate)*	660.0	477.0
CN (aliphatic)*	2504.0	1810.0
CN (aromatic)*	2133.0	1553.0
Cl	873.9	643.1
Br	217.2	189.5
I	−17.2	40.5
Branch in a carbon chain	−132.7	−94.7
Benzene ring bonds	5788.6	4002.4
Cyclohexane ring bonds	1166.1	793.7
Cyclohexene ring bonds*	2860.0	1967.0
O (carbonate)**	550	420
F**	530	380
Sn**	−1440	−960
NO_2 (nitro)**	1680	1230
Double bond**	1470	1010
Double bond*	1670	1174
Triple bond**	3580	2510
Triple bond*	3344	2334
Pyridine ring bonds**	5900	4130
Furane ring bonds**	4260	2950

* From reference 23.
** Provisional values.

while the limiting form applicable to liquids of high molecular weight is given by

$$\delta = \rho^{5/6}\left(\frac{\Delta\lambda_{ir}}{M_r}\right)^{2/3} \qquad (18)$$

Small. In 1953 Small (24) proposed that the quantity $(V\Delta E_v)^{1/2}$ could be obtained as the sum of atomic and group increments; these were termed molar-attraction constants and denoted by the symbol *F;* the values of *F* derived by Small are listed in *Table 3*. Using the definition of the molar-attraction constant in conjunction with *Eq 1*, the solubility parameter can be written as

$$\delta = \left[\frac{\sum_i \Delta f_i}{V}\right] \qquad (19)$$

and the asymptotic limit of this expression for the case of high molecular weight polymers is

$$\delta = \rho\left(\frac{\Delta f_{ir}}{M_r}\right) \qquad (20)$$

In common with Dunkel's method, this system will provide estimates of δ only for a temperature of 25°C, since, as can be expected, the Δf_i values are functions of the temperature. Small's system has been the most widely used method for the estimation of δ.

Table 3. Molar-Attraction Constants at 25°C (24)

Atom or group	Δf_i, cal$^{1/2}$cm$^{3/2}$	Atom or group	Δf_i, cal$^{1/2}$cm$^{3/2}$
CH_3	214	H (variable)	80-100
CH_2	133	O (ether)	70
CH (single-bonded)	28	CO (ketones)	275
C (single-bonded)	−93	CO_2 (esters)	310
CH_2= (double-bonded)	190	CN	410
—CH= (double-bonded)	111	Cl (mean)	260
C= (double-bonded)	19	Cl (single)	270
CH≡C	285	Cl (twinned as in CCl_2)	260
—C≡C—	222	Cl (triple as in CCl_3)	250
Phenyl	735	Br (single)	340
Phenylene (o, m, p)	658	I (single)	425
Naphthyl	1146	CF_2 } n-fluorocarbons only	150
Ring, 5-membered	105-115	CF_3 } n-fluorocarbons only	274
Ring, 6-membered	95-105	S (sulfides)	225
Conjugation	20-30	SH (thiols)	315
		NO_3 (nitrate)*	440
		NO_2 (aliphatic nitro)*	440
		PO_4 (organic phosphates)	500

* Provisional values.

Rheineck and Lin. Yet another system of atomic and group additive increments was developed by Rheineck and Lin (25). They observed that for various homologous series of 1, *n*-alkane compounds, both ΔE_v and V could be estimated using atomic and group increments. Thus, they proposed that the molar volume of a 1-substituted *n*-alkane could be estimated using,

$$V = \Delta v_{CH_3} + \Delta v_z + (n-1)\Delta v_{CH_2} \qquad (21)$$

where Δv_{CH_3}, Δv_z and Δv_{CH_2} are the molar volume contributions of the end methyl, the *z*-substituent and the methylene group respectively. In addition, the ΔE_v value for the same alkanes could be estimated using the following expression

$$\Delta E_v = \Delta e_{CH_3} + \Delta e_z + (n-1+\mu_z)\Delta e_{CH_2} \qquad (22)$$

where Δe_{CH_3}, Δe_z and Δe_{CH_2} are the molar contributions to the energy of vaporization from the end methyl group, the *z*-substituent and the methylene group respectively and μ_z is a correction factor for the chain length whose numerical value depends on the chemical nature of *z*. Values for the various atomic and group increments are listed in *Table 4*.

The solubility parameters for the 1-substituted *n*-alkanes based on *Eqs 21* and *22* can be written as

$$\delta = \left(\frac{\Delta e_{CH_3} + \Delta e_z + (n-1+\mu_z)\Delta e_{CH_2}}{\Delta v_{CH_3} + \Delta v_z + (n-1)\Delta v_{CH_2}} \right)^{1/2} \qquad (23)$$

In common with both Dunkel and Small, this system is only applicable to the estimation of δ at 25°. On the other hand, contrary to Dunkel and Small which require knowledge of both chemical structure and density in order to estimate δ, this method requires only the knowledge of the chemical structure. However, the method is apparently limited to 1-substituted *n*-alkanes since the dependence of the additional chain length correction parameter μ_z on chemical structure has not been reported.

Table 4. Atomic and Group Contributions to the Energy of Vaporization and Molar Volume at 25°C (25)

Atom or group	Δe_i, cal/mole	$\Delta\mu_z$, cal/mole/no. C-atoms	Δv_i, cm^3/mole
CH	970	0	−0.5
CH_2	1230	0	16.5
CH_3	990	0	34.0
OH	7830	−0.08	8.7
NH_2	2570	−0.09	19.0
Cl	2790	−0.06	24.0
CHO	4340	−0.17	26.0
COOH	7830	+0.22	27.0
CH_3CO	—	—	42.5
$CH=CH_2$	2000	0	44.0
CH_3COO	5550	−0.10	50.5
$CH(CH_3)_2$	2950	0	67.5
Phenyl	7450	−0.22	75.0
Cyclohexyl	7040	−0.22	95.0

Proposed Method

Based upon an examination of a vast amount of data on simple liquids, it was found that a general system for estimating both ΔE_v and V could be set up simply by assuming

$$\Delta E_v = \sum_i \Delta e_i \qquad (24)$$

and

$$V = \sum_i \Delta v_i \qquad (25)$$

where the Δe_i and Δv_i are the additive atomic and group contribution for the energy of vaporization and molar volume respectively. These contributions applicable at a temperature of 25°C are listed in *Table 5*.

Of special interest is the large number of atoms and groups for which the additive increments have been evaluated. In addition, the evaluation has also been carried out for several metals which contain

Table 5. Atomic and Group Contributions to the Energy of Vaporization and the Molar Volume at 25°C

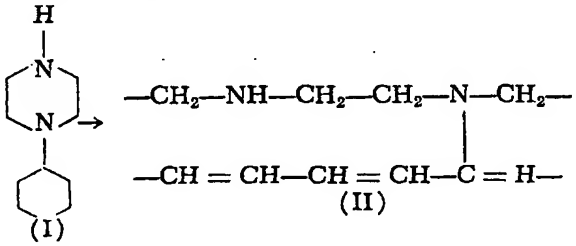
Atom or group	Δe_i, cal/mole	Δv_i, cm³/mole
CH_3	1125	33.5
CH_2	1180	16.1
CH	820	−1.0
C	350	−19.2
$H_2C=$	1030	28.5
—CH=	1030	13.5
C=	1030	−5.5
HC≡	920	27.4
—C≡	1690	6.5
Phenyl*	7630	71.4
Phenylene (o, m, p)*	7630	52.4
Phenyl (trisubstituted)*	7630	33.4
Phenyl (tetrasubstituted)*	7630	14.4
Phenyl (pentasubstituted)*	7630	−4.6
Phenyl (hexasubstituted)*	7630	−23.6
Ring closure 5 or more atoms	250	16
Ring closure 3 or 4 atoms	750	18
Conjugation in ring for each double bond	400	−2.2
Halogen attached to carbon atom with double bond	−20 percent of Δe_i of halogen	4.0
CO_3 (carbonate)	4200	22.0
COOH	6600	28.5
CO_2	4300	18.0
CO	4150	10.8
CHO (aldehyde)	5100	22.3
CO_2CO_2 (oxalate)	6400	37.3
C_2O_3 (anhydride)	7300	30.0
HCOO (formate)	4300	32.5
$CONH_2$	10000	17.5
CONH	8000	9.5
CON	7050	−7.7
HCON	6600	11.3
HCONH	10500	27.0
COCl	5000	38.0
NH_2	3000	19.2
NH	2000	4.5
N	1000	−9.0
—N=	2800	5.0
CN	6100	24.0
NO_2 (aliphatic)	7000	24.0
NO_2 (aromatic)	3670	32.0
NO_3	5000	33.5
NO_2 (nitrite)	2800	33.5
SCN	4800	37.0
NCO	6800	35.0
NF_2	1830	33.1
NF	1210	24.5
O	800	3.8
OH	7120	10.0
OH (disubstituted or on adjacent C atoms)	5220	13.0
PO_4	5000	28.0
PO_3	3400	22.7
SH	3450	28.0
S	3380	12
S_2	5700	23.0
SO_3	4500	27.6
SO_4	6800	31.6
F	1000	18.0
F (disubstituted)	850	20.0
F (trisubstituted)	550	22.0
CF_2 (for perfluoro compounds)	1020	23.0
CF_3 (for perfluoro compounds)	1020	57.5
Cl	2760	24.0
Cl (disubstituted)	2300	26.0
Cl (trisubstituted)	1800	27.3
Br	3700	30.0
Br (disubstituted)	2950	31.0
Br (trisubstituted)	2550	32.4
I	4550	31.5
I (disubstituted)	4000	33.3
I (trisubstituted)	3900	37.0
B	3300	−2.0
Al	3300	−2.0
Ga	3300	−2.0
In	3300	−2.0
Tl	3300	−2.0
Si	810	0
Ge	1930	−1.5
Sn	2700	1.5
Pb	4100	2.5
P	2250	−1.0
As	3100	7.0
Sb	3900	8.9
Bi	5100	9.5
Se	4100	16.0
Te	4800	17.4
Zn	3460	2.5
Cd	4250	6.5
Hg	5450	7.5

Table 5. (Cont'd.)

* These values listed for convenience. The values reported for Δe_i and Δv_i can be evaluated from the appropriate entries in the table.

only metal-carbon bonds, i.e., for organometallic compounds. Furthermore, it has been found that both ΔE_v and V for cyclic compounds can be estimated from the properties of a linear compound having the same chemical structure; this is accomplished by adding a cyclization increment to both ΔE_v and V of the linear compound.

For example, suppose one wanted to estimate both δ and V for a liquid such as N-phenyl piperazine (I). The linear compound which is



used for estimating these properties is formed by cutting bonds in the ring compound in such a manner that any functional group listed in *Table 5* and present in the ring itself remains intact; the reason for this provision is the fact that the increments listed in the table for some groups are not simply the sum of the atomic contributions, i.e., the value for a carboxylate group, COO, is not obtained by summing the values of carbon and 2 ether oxygen atoms.

Considering the linear compound II, the following table can be set up:

Group	Δe_i, cal/mole	Δv_i, cm³/mole
4 CH_2	4720	64.4
1 NH	2000	4.5
1 N	1000	−9.0
5 CH=	5150	67.5
1 C=	1030	−5.5
3 conjugated double bonds	1200	−6.6
2 6-membered rings	500	32.0
	15,600	147.3

Hence, for the cyclic compound the estimate for δ and V are 10.30 and 147.4. The values obtained experimentally and listed by Hoy (17) are 10.55 and 152.1.

Experience using this method has shown that deviations between the experimentally measured ΔE_v and V and the estimated values are generally less than about 10 percent. Major deviations, when they occur, are usually limited to the first few members of a homologous series.

A problem occurs when the compound in question has either a T_g or a T_m above room temperature in that the estimates for both V and δ refer to the supercooled liquid rather than to the glass or to the crystalline phase. *Figure 1* shows that the estimates obtained using the increments from *Table 5* for V would be smaller than the experimentally obtained values for both a glass or a crystal. On the other hand, the estimates for ΔE_v obtained using the increments would be greater than the experimental values.

For high molecular weight polymers which have a T_g greater than 25°C, this divergence in the V values can be taken in account by the introduction of small correction factors, namely,

$$\Delta v_i = 4n \quad , \quad n < 3$$
$$\Delta v_i = 2n \quad , \quad n \geqq 3 \qquad (26)$$

where n is the number of main chain skeletal atoms in the smallest repeating unit of the polymer. This includes all the skeletal atoms in a ring system which may be part of the main chain, i.e., for the phenylene group in poly(ethylene terephthalate) n is taken equal to 6 and n has the value 12 for the repeating unit.

As an example, consider poly(hexamethylene adipamide) which has a T_g of 50°C (26), an average density of the amorphous material equal to 1.08 g/cm³ and a smallest repeating unit of $(CH_2)_6NHCO(CH_2)_4NHCO$. The V value calculated using the increments from *Table 5* is

Group	Δv_i, cm³/mole
10 CH_2	161
2 NHCO	19
14 main chain skeletal atoms	28
	208

Hence, the predicted V is 208 cm³/mole which is close to the experimental value of 209 cm³/mole.

As an approximate rule of thumb, the relationship between the molar volume of the liquid and crystalline phase, V_c, can be taken as

$$V = (1 + 0.13x)V_c \qquad (27)$$

where x is the degree of crystallization. Applied to poly(hexamethylene adipamide) this expression predicts, taking V equal to 208 cm³/mole, V_c to have the value 184 cm³/mole compared to the measured value of 185 cm³/mole (26).

From the very limited data available, it does not seem that the estimates for ΔE_v for a glass vary appreciably from that calculated for the liquid. Hence, provisionally and as an unavoidable approximation, one can assume that ΔE_v for the glass and the liquid are the same.

Using *Eqs 24* and *25*, the solubility parameters for liquids at 25°C can be written

$$\delta = \left[\frac{\sum_i \Delta e_i}{\sum_i \Delta v_i} \right]^{1/2} \qquad (28)$$

and the limiting form for liquids of high molecular weight becomes

$$\delta = \left(\frac{\Delta e_{ir}}{\Delta v_{ir}} \right)^{1/2} \qquad (29)$$

Equations 28 and *29* require only a knowledge of the chemical structure in order to estimate δ. However, as was true with the systems proposed by Dunkel, Small and Rheineck and Lin, the proposed method is applicable only at a single temperature. However, as will now be demonstrated, it is possible to circumvent this difficulty.

Duggar (27) has shown that for both polar and non-polar liquids, the dependence of the orthobaric densities $(\rho_L - \rho_v)$ on temperature is accurately given by

$$\frac{\rho_{L2} - \rho_{v2}}{\rho_{L1} - \rho_{v1}} = \left(\frac{T_c - T_2}{T_c - T_1} \right)^{0.3} \qquad (30)$$

We can neglect ρ_v compared to ρ_L and in so doing dispense with the subscript L. Using this expression and *Eq 2*, the terms involving temperature can be eliminated and hence

$$\frac{\Delta H_{v,T_2}}{\Delta H_{v,T_1}} = \left(\frac{\rho_2}{\rho_1} \right)^{1.27} \qquad (31)$$

This equation can also be obtained from *Eq 12* used by Bowden and Jones. Using the fact that $\Delta H_v = \Delta E_v + RT$, *Eq 31* becomes

$$\delta_2^2 = \delta_1^2 \left(\frac{V_1}{V_2} \right)^{2.27} + \frac{R}{V_2} \left[T_1 \left(\frac{V_1}{V_2} \right)^{1.27} - T_2 \right] \qquad (32)$$

When the temperatures T_1 and T_2 do not differ by more than about 150° and when both are at or below the normal boiling point of the liquid, then the second term on the right hand side will be negligible compared to the first and hence

$$\delta_2 = \delta_1 \left(\frac{V_1}{V_2}\right)^{1.13} = \delta_1 \left(\frac{\rho_2}{\rho_1}\right)^{1.13} \qquad (33)$$

This expression provides a means of estimating the temperature dependence of the solubility parameter from a knowledge of the temperature dependence of the density. Another convenient relationship can be developed which involves temperature directly. Over small ranges in temperature, the dependence of volume on temperature is given by

$$V_2 = V_1 [1 + \alpha(T_2 - T_1)] \qquad (34)$$

where α is the cubical coefficient of expansion. Substituting this relationship into *Eq 33* and expanding the term in parentheses, there is obtained

$$\delta_2 = \delta_1 [1 + 1.13\alpha(T_1 - T_2)] \qquad (35)$$

This particularly simple expression is valid to within about 2 percent provided that $T_1 - T_2$ is less than about 50°.

SUMMARY

A system of additive atomic and group increments has been developed which permit the estimation of both the solubility parameter and the molar volume for both liquids and high molecular weight amorphous polymers and requires only a knowledge of the chemical structure. In addition, equations have been derived which allow one to estimate the temperature dependence of δ from a knowledge of the temperature dependence of the density.

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